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RABIES

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Rabies is a viral infection transmitted in the saliva of infected mammals. The virus enters the central nervous system of the host, causing an encephalomyelitis that is almost always fatal. Although rabies among humans has not been reported for the past 50 years in Louisiana, every year approximately 300 to 600 persons receive postexposure prophylaxis. To appropriately manage potential human exposures to rabies, the risk of infection must be accurately assessed. Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed.

Epidemiology

The disease is caused by a virus that is usually introduced into the body by way of an animal bite or by an animal licking mucosa, damaged skin (eczema for example), or open wounds. Other methods of transmission have been documented on rare occasions. In addition to saliva and neural tissue, rabies virus also has been detected in the kidney, prostate, pancreas and other tissues and body fluids.

The last case of human rabies in Louisiana occurred in 1953. Rabies is now primarily a disease found in wild animals. Wild animals, especially skunks, continue to be the most commonly affected animals. Cases of animal rabies used to be limited mostly to the northern and north central part of the state. Since 1995, there has been a southern migration of skunk rabies into the southwestern (Lafayette region) part of the state. Bat rabies has been found throughout the state. There are occasionally positive results from domestic animals, usually dogs. Rodents (rats, mice, squirrels), and rabbits rarely test positive for rabies, have not been found to transmit rabies and therefore, are not tested under usual circumstances.

Types of Exposure

Rabies is transmitted only when the virus is introduced into bite wounds or open cuts in skin or onto mucous membranes. If no exposure has occurred (i.e., no bite or nonbite exposure), postexposure prophylaxis is not necessary. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure -- bite and nonbite -- should be considered.

Bite

Any penetration of the skin by teeth constitutes a bite exposure. All bites, regardless of location, represent potential risks of rabies transmission. Bites by some animals, such as bats, can inflict minor injury and thus be undetected.

Nonbite

Nonbite exposures from terrestrial animals rarely cause rabies. However, occasional reports of transmission by nonbite exposure suggest that such exposures constitute sufficient reason to consider postexposure prophylaxis. The nonbite exposures of highest risk appear to be among persons exposed to large amounts of aerosolized rabies virus and surgical recipients of organs transplanted from patients who have died of rabies. Two cases of rabies have been attributed to probable aerosol exposures in laboratories, and

two cases of rabies have been attributed to possible airborne exposures in caves containing millions of free-tailed bats in Texas.

The contamination of open wounds, abrasions, mucous membranes, or theoretically, scratches, with saliva or other potentially infectious material (such as neural tissue) from a rabid animal also constitutes a non-bite exposure. Other contact by itself, such as petting a rabid animal and contact with blood, urine, or feces (e.g., guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Because the rabies virus is inactivated by desiccation and ultraviolet irradiation, in general, if the material containing the virus is dry, the virus can be considered noninfectious.

Domestic Dogs, Cats and Ferrets

The likelihood of rabies in a domestic animal varies by region. In the continental United States, rabies among dogs is reported most commonly along the United States-Mexico border, and sporadically in areas of the United States with enzootic wildlife rabies. During most of the 1990s, more cats than dogs were reported rabid in the United States. The majority of these cases were associated with the epizootic of rabies among raccoons in the eastern United States. The large number of rabies-infected cats might be attributed to fewer cat vaccination laws, fewer leash laws and the roaming habits of cats. In many developing countries, dogs are the major vector of rabies; exposures to dogs in such countries represent an increased risk of rabies transmission. Ferrets are now considered in the same category with dogs and cats.

Bats

Rabid bats have been documented in the 49 continental states and throughout Louisiana. Bats are increasingly implicated as important wildlife reservoirs for variants of rabies virus transmitted to humans. Recent epidemiologic data suggest that transmission of rabies virus can occur from minor, seemingly unimportant, or unrecognized bites from bats. The limited injury inflicted by a bat bite (in contrast to lesions caused by terrestrial carnivores), and an often inaccurate recall of the exact exposure history might limit the ability of health-care providers to determine the risk of rabies resulting from an encounter with a bat. Human and domestic animal contact with bats should be minimized; bats should never be handled by untrained and unvaccinated persons, or be kept as pets.

In all instances of potential human exposures involving bats, the bat in question should be safely collected, if possible, and submitted for rabies diagnosis.

The following are the species of bats that can be found in Louisiana: Mexican Freetail, Big Brown Bat, Eastern Red Bat, Hoary Bat, Northern Yellow Bat, Seminole Bat, Southeastern Myotis, Eastern Pipistrelle, Evening Bat, Rafinesque's Big Eared Bat and Silver Haired Bat.

Wild Terrestrial Carnivores

Raccoons, skunks, foxes, and coyotes are the terrestrial animals most often infected with rabies. All bites by such wildlife must be considered as possible exposure to the rabies virus.

Other Wild Animals: Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats and mice), and lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and have not been known to transmit rabies to humans.

From 1990 through 1996, in areas of the country where raccoon rabies was enzootic, woodchucks accounted for 93% of the 371 cases of rabies among rodents reported to Centers of Disease Control and Prevention (CDC). The offspring of wild animals crossbred to domestic dogs and cats (wild animal hybrids) are considered wild animals. Because the period of rabies virus shedding in these animals is unknown, these animals should be euthanized and tested, rather than confined and observed when they bite humans. Wild animals and wild animal hybrids should not be kept as pets.

Consumption of meat from an infected animal is known to occur, chiefly in nature as carnivorous animals eat sick or dead rabid animals. An average of 150 rabid cattle has been reported to CDC in the United States each year since 1990. In addition to concerns about rabies transmission from animals to humans through bites, rabid livestock raise the potential for foodborne transmission. The National Association of State Public Health Veterinarians recommends against consuming tissues and milk from rabid animals.

In the United States, the law says that animals showing neurological conditions are not to be consumed after seven days after presumed infection date. The meat (muscle) of an animal killed during clinical rabies would not be expected to contain much rabies virus (although details of the pantropism of the vampire bat variant of rabies virus in other species are not thoroughly described). **Thoroughly** cooked, dried or salted meat should present no risk to the consumer due to the labile nature of the virus. The real risk is to the processors -- those who cut up the animal, chiefly if they handled the brain, spinal cord or salivary glands.

Transmission by milk is rare. Anecdotal reports exist of rabies transmission by ingestion of milk from rabid animals (e.g., from a rabid sheep to a nursing lamb). In these reports, the more conventional routes (e.g., bite or mucous membrane exposure) could not be completely excluded. Transmission of rabies virus in unpasteurized milk is theoretically possible. The risk could be defined better if samples of milk and mammary tissue were collected from rabid livestock and assayed for the presence, viability and infectivity of rabies virus. Regardless of the amount of viable rabies virus that may be shed in cows' milk, the theoretical risk for transmission of rabies from this route can be eliminated if all dairy products are pasteurized before consumption. However, because rabies virus is inactivated by temperatures below those used for cooking and pasteurization, eating cooked meat or drinking pasteurized milk from a rabid animal is not an indication for 'Post-Exposure Prophylaxis' (PEP).

Human-to-Human Transmission

Human-to-human transmission has occurred among eight recipients of transplanted corneas from donors and among four recipients of other organs from one single donor. Investigations revealed that each of the donors had died of an illness compatible with, or proven to be rabies.

Apart from transplants, bite and nonbite exposures inflicted by infected humans could theoretically transmit rabies, but no laboratory-diagnosed cases occurring under such situations have been documented. Two nonlaboratory-confirmed cases of human-to-human rabies transmission in Ethiopia have been described. The reported route of exposure in both cases was direct salivary contact from another human (a bite and a kiss). Routine delivery of health care to a patient with rabies is not an indication for PEP unless exposure of mucous membranes or nonintact skin to potentially infectious body fluids has occurred.

Susceptibility to rabies

- Very high for wolves, foxes, coyotes, kangaroo rats, cotton rats, jackals, voles
- High for hamsters, skunks, raccoons, domestic cats, rabbits, bats, cattle
- Moderate for dogs and primates
- Low for opossums

The incubation period for rabies varies **from a few days to more than 19 years**, although 75% of patients become ill in the first 90 days after exposure.

Clinical Description

The actual disease starts only after the CNS has been invaded.
The prodromal stage of two to four days includes fever, malaise, headache and nausea. This is followed by an array of neurological signs:

- Hyperexcitability

- Hydrophobia
- Aerophobia: spasms of pharyngeal muscle after fanning the face
- Sensitivity to light, sound and other sensory stimuli
- Increased muscle tension and tics followed by painful muscle contractions (spasms) caused by swallowing (hydrophobia)
- Increased sweating, salivation or lacrimation resulting from involvement of the sympathetic system
- Ascending paralysis, particularly in bat rabies
- Confusion, delirium, coma

Without treatment, death occurs within two to six days often from paralysis of respiratory muscles.

Human rabies infections are divided into two forms: furious (or encephalitic), and paralytic (or dumb). The furious form presents with the hydrophobia, delirium and agitation that create the common picture of rabies. About a fifth of patients presents with the paralytic form and have little clinical evidence of cerebral involvement until late in their course. The spinal cord and brain stem bear the brunt of the illness in the paralytic form. In contrast to the furious form, paralytic rabies patients lack hydrophobia, aerophobia, hyperactivity, or seizures. Their initial findings suggest an ascending paralysis, resembling acute inflammatory polyneuropathy (the Guillain-Barre syndrome), or a symmetric quadriparesis. Weakness may be more severe in the extremity where the virus was introduced. Meningeal signs (headache, neck stiffness) may be prominent despite a normal sensorium. As the disease progresses, the patient becomes confused and then declines into coma.

The major differential for furious rabies is another viral encephalitis. In the absence of exposure to a rabid animal, and if hydrophobia and hyperactivity are not prominent, it may be difficult to distinguish among these possibilities. CSF and electroencephalographic findings in rabies may mimic those of herpes simplex encephalitis; some patients receive empirical therapy with acyclovir while awaiting a more secure diagnosis. Tetanus or strychnine poisoning should be considered. Paralytic rabies may resemble acute inflammatory polyneuropathy, transverse myelitis, or poliomyelitis.

Laboratory Tests

Diagnosis of rabies in animals relies on examination of the brain:

- Detection of Negri bodies: Negri bodies are cytoplasmic inclusions made of rabies virus ribonucleoprotein which can be stained (Giemsa, Mann staining techniques) and observed under the light microscope.
- Detection of viral particles by fluorescence antibody test (FA): A fluorescein dye conjugated to a rabies antiglobulin is applied on a smear of the brain. Fluorescence concentrates on rabies viral particles. The test is rapid and reliable in the hands of an experienced technician. During life, FA tests may detect viral particles in a skin biopsy (back of the neck at the hairline), corneal impression or buccal mucosal scraping.
- Detection of rabies antibodies in the CSF: Vaccination alone does not trigger production of antibodies in the CSF. Antibodies appear in the blood from 8 to 10 days after immunization.

Tests for suspected human cases:

1. Direct fluorescent antibody

When requesting direct fluorescent antibody on a clinical specimen (preferably brain tissue or nerves surrounding hair follicles in the nape of the neck).

2. Culture (saliva, cerebrospinal fluid, or central nervous system tissue). Not routinely available at the State Laboratory; available in limited cases, with prior approval, through CDC.

3. Antibody titer (submit serum or cerebrospinal fluid, from unvaccinated persons only). Not routinely available at the State Laboratory.

When a case is suspected in a human, CSF, blood, saliva and/or appropriate skin biopsies need to be sent to CDC through the Central Laboratory in New Orleans. Contact the Infectious Disease Epidemiology Section and the OPH Laboratory on the proper handling and shipping of specimens prior to submitting the samples.

Tests for suspected animal cases:

1. Direct fluorescent antibody test (submit specimen: preferably central nervous system tissue).
2. Cultures are only done if results of the DFA are equivocal. Not routinely available at the State Laboratory. Do not wait for the results of the culture to decide on post exposure prophylaxis.

Surveillance

Rabies in humans or animals is a reportable condition by phone within 24 hours of suspecting the diagnosis.

Case Definition

A case of human rabies is defined as an illness characterized by acute encephalomyelitis that almost always progresses to coma or death and is laboratory confirmed.

Laboratory confirmation: A case of human rabies can be confirmed by:
1. Detection by direct fluorescent antibody of viral antigens in a clinical specimen, or
2. Isolation (in cell culture or in a laboratory animal) of rabies virus from saliva, cerebrospinal fluid (CSF), or central nervous system tissue, or
3. Identification of a rabies-neutralizing antibody titer >5 (complete neutralization) in the serum or CSF of an unvaccinated person.

A case of animal rabies can be confirmed by
1. Positive direct fluorescent antibody test
2. Isolation of rabies virus (in cell culture or in a laboratory animal)

Investigation of a human case

The purpose of this investigation is to confirm a suspected case of human rabies as quickly as possible, to identify and test the suspected source of exposure, i.e., wild or domestic animal, and to initiate prophylactic treatment immediately to exposed individuals.

- Because of the serious nature of this disease and the difficulty of diagnosing, the notification of a case of human rabies would come from a major hospital or medical center.
- The reporting source may request the assistance of the health department in sending material to CDC for testing. Consult the Infectious Disease Epidemiology Section and the OPH Laboratory on the appropriate handling of specimens.
- Identify the source of the human infection. If the source is identified as an animal, ensure that the biting animal is managed properly.
- Identify all individuals and animals exposed to the implicated animal.
- Ensure that exposed individuals obtain proper medical care.
- Ensure that exposed animals are properly handled.
- Attempt to identify additional infections in animals in the surrounding area. This will be carried out in collaboration with Veterinary services.

Investigation of an exposure to a suspected rabid animal

A human exposure to a potential source of rabies is defined as a bite or scratch or the licking of mucosa or open wound by an animal species commonly associated with the transmission of rabies.

Human exposure to parenteral animal rabies vaccines does not constitute a risk for rabies infection. However, human exposure to vaccinia-vectored oral rabies vaccines should be reported to OPH.

The purpose of this investigation of an exposure to a suspected rabid animal is to identify and test the suspected animal (wild or domestic animal), and initiate prophylactic treatment immediately to exposed individuals as each situation warrants.

- Identify the animal(s) involved in the bite, scratch, etc.
- Immediately and thoroughly washing of all bite wounds and scratches with soap and water, and a virucidal agent such as a povidone-iodine solution irrigation, are important measures for preventing rabies. In studies of animals, thorough wound cleansing alone without other postexposure prophylaxis has been shown to reduce markedly the likelihood of rabies.
- Ensure that tetanus prophylaxis and measures to control bacterial infection also are administered as indicated.
- The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infections.
- When indicated, recommend concurrent use of both human rabies immune globulin (HRIG), and rabies vaccine.

Persons who have been bitten by animals suspected or proven to be rabid should begin PEP immediately. Incubation periods of greater than one year have been reported in humans. Thus, when a documented or likely exposure has occurred, postexposure prophylaxis is indicated regardless of the length of the delay, provided the clinical signs of rabies are not present.

In general, HRIG and rabies vaccine should be used in the following situations:

- if the biting animal tests positive for rabies
- if the wild animal (such as fox, bat, skunk, raccoon, wolf, etc. including hybrids) cannot be located for testing
- if the situation surrounding the bite indicates that the animal possibly could be rabid (sick, aggressive or unusual behavior), and the animal was not tested, or the test results were equivocal
- if the bite was unprovoked and the animal was not located
- Wild animals, (including hybrids), should be humanely killed and tested. Observation of wild animals for 10 days is NOT recognized as an appropriate measure.
- Domestic pets, (cats, dogs, ferrets) should be:
  - quarantined and observed for 10 days by an authorized party, usually (instead of immediately testing the animal for rabies). If the animal becomes ill with symptoms of rabies or dies from a rabies-like illness during the observation period, the animal should be tested for rabies. Assure the person bitten that if the animal is found to be positive for rabies during the observation period, there is enough time to initiate PEP to prevent human rabies.
  - sacrificed and their head sent to an OPH laboratory
- Animals such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, rabbits, hares, and opossums are usually killed during an encounter with a rabid animal and therefore are not a source of infection. Their head will not be accepted for testing unless cleared by consultation with the Infectious Disease Epidemiology Section.

See section on post-exposure prophylaxis for more details.

Rabies immunizing agents

Two types of rabies immunizing products are available in the United States.

- Rabies vaccines induce an active immune response that includes the production of neutralizing antibodies. This antibody response requires approximately 7-10 days to develop and usually persists for greater than or equal to 2 years.
- Rabies immune globulin (RIG) provides a rapid, passive immunity that persists for only a short time (half-life of approximately 21 days).

In all postexposure prophylaxis regimens, except for persons previously immunized, both products should be used concurrently.

Vaccines Licensed for Use in the United States

Four formulations of three inactivated rabies vaccines are currently licensed for preexposure and postexposure prophylaxis in the United States. When used as indicated, all three types of rabies vaccines are considered equally safe and efficacious. The potency of one dose is greater than or equal to 2.5 international units (IU) per 1.0 mL of rabies virus antigen, which is the World Health Organization recommended standard. A full 1.0-mL dose can be used for both preexposure and postexposure prophylaxis. However, only the Imovax Rabies I.D. vaccine (human diploid cell vaccine {HDCV}) has been evaluated and approved by the Food and Drug Administration (FDA) for the intradermal dose and route for preexposure vaccination. Therefore, rabies vaccine adsorbed (RVA), and purified chick embryo cell vaccine (PCEC) should not be used intradermally. Usually, an immunization series is initiated and completed with one vaccine product. No clinical studies have been conducted that document a change in efficacy or the frequency of adverse reactions when the series is completed with a second vaccine product.

Human Diploid Cell Vaccine (HDCV)

HDCV is prepared from the Pitman-Moore strain of rabies virus grown on MRC-5 human diploid cell culture, concentrated by ultrafiltration and inactivated with beta-propiolactone. It is supplied in two forms:

Intramuscular (IM) administration, a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying diluent to a final volume of 1.0 mL just before administration.

Intradermal (ID) administration, a single-dose syringe containing lyophilized vaccine that is reconstituted in the syringe to a final volume of 0.1 mL just before administration.

Rabies Vaccine Adsorbed (RVA)

RVA was developed and is currently manufactured and distributed in the state of Michigan by BioPort Corporation. The vaccine is prepared from the Kissling strain of Challenge Virus Standard (CVS) rabies virus adapted to fetal rhesus lung diploid cell culture. The vaccine virus is inactivated with betapropiolactone and concentrated by adsorption to aluminum phosphate. Because RVA is adsorbed to aluminum phosphate, it is liquid rather than lyophilized. It is approved for IM administration only as a 1.0-mL dose.

Purified Chick Embryo Cell Vaccine (PCEC)

PCEC became available in the United States in autumn 1997. It is prepared from the fixed rabies virus strain Flury LEP grown in primary cultures of chicken fibroblasts. The virus is inactivated with betapropiolactone and further processed by zonal centrifugation in a sucrose density gradient. It is formulated for IM administration only. PCEC is available in a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying diluent to a final volume of 1.0 mL just before administration.

Rabies Immune Globulin Licensed for Use in the United States

The two RIG products, BayRabTM and Imogam Rabies-HT, are antirabies immunoglobulin (IgG) preparations concentrated by cold ethanol fractionation from plasma of hyperimmunized human donors. Rabies

neutralizing antibody, standardized at a concentration of 150 IU per mL, is supplied in 2-mL (300 IU) vials for pediatric use and 10-mL (1,500 IU) vials for adult use; the recommended dose is 20 IU/kg body weight. Both RIG preparations are considered equally efficacious when used as described in this report (see Treatment of Wounds and Immunization).

Human rabies vaccine	Product name	Manufacturer	Ordering
Human diploid cell vaccine (HDCV) Intramuscular Intradermal	 Imovax Rabies Imovax Rabies I.D	Pasteur-Merieux	(800) VACCINE or (800) 822-2463
Purified chick embryo cell	RabAvert	Novartis	Novartis (800) 244-7668 McKesson MedSurg (800) 950-9229 ASD Healthcare (800)746-6273 FFF Enterprises (800) 843-7477 Cardinal (800) 964-5227
Rabies immune globulin (RIG)	Imogam Rabies-HT	Pasteur-Merieux	(800) VACCINE or (800) 822-2463
Rabies immune globulin (RIG)	BayRab	Bayer Corp	(800) 288-8370

Where to find vaccine and immuneglobulin

Vaccine and immuneglobulin are available in some large pharmacies and in LSU Medical Center pharmacies.

Primary Or Preexposure Vaccination

Preexposure vaccination should be offered to persons in high-risk groups, such as

- veterinarians
- animal handlers
- certain laboratory workers.
- Preexposure vaccination also should be considered for other persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies.
- International travelers might be candidates for preexposure vaccination if they are likely to come in contact with animals in areas where dog rabies is enzootic and immediate access to appropriate medical care, including biologics, might be limited.

Routine preexposure prophylaxis for other situations might not be indicated.

Preexposure prophylaxis is administered for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional therapy after a rabies exposure, it simplifies therapy by eliminating the need for RIG and decreasing the number of doses of vaccine needed -- a point of particular importance for persons at high risk for being exposed to rabies in areas where immunizing products might not be available or where they might be at high risk for adverse reactions. Second, pre- exposure prophylaxis might protect persons whose postexposure therapy is delayed. Finally, it might provide protection to persons at risk for inapparent exposures to rabies.

Risk category	Nature of risk	Typical populations	Preexposure recommendations
Continuous	Virus present continuously often in high concentrations. Specific exposures likely to go unrecognized	Rabies research laboratory workers;* rabies biologics production workers	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure	Rabies diagnostic labworkers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent (greater than population at large)	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas with low rabies rates. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-epizootic areas.	No vaccination necessary.

Intramuscular Primary Vaccination

Three 1.0-mL injections of HDCV, RVA, or PCEC should be administered intramuscularly (deltoid area) -- one injection per day on days 0, 7, and 21 or 28. In a study in the United States, greater than 1,000 persons received HDCV according to this regimen. Antibody was found in serum samples of all subjects when tested by the rapid fluorescent focus inhibition test (RFFIT). Studies with other products have produced comparable results.

Intradermal Primary Vaccination

A regimen of three 0.1-mL ID doses of HDCV, one each on days 0, 7, and 21 or 28, is also used for preexposure vaccination as an alternative to the 1.0-mL IM regimen for rabies preexposure prophylaxis with HDCV. A single dose of lyophilized HDCV (Imovax Rabies I.D.) is available prepackaged for reconstitution in the syringe just before administration. The syringe is designed to deliver 0.1 mL of HDCV reliably and has been approved by the FDA since 1986. The 0.1-mL ID doses, administered in the area over the deltoid (lateral aspect of the upper arm) on days 0, 7, and 21 or 28, are used for primary preexposure vaccination. One 0.1-mL ID dose is used for routine preexposure booster vaccination. The 1.0-mL vial is not approved for multidose ID use. RVA and PCEC are not approved for and should not be administered intradermally.

Preexposure Booster Doses of Vaccine

Persons who work with rabies virus in research laboratories or vaccine production facilities (continuous risk category are at the highest risk for inapparent exposures. Such persons should have a serum sample tested for rabies antibody every 6 months. Booster doses (IM or ID) of vaccine should be administered to maintain a serum titer corresponding to at least complete neutralization at a 1:5 serum dilution by the RFFIT. The frequent-risk category includes other laboratory workers (e.g., those performing rabies diagnostic testing), spelunkers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic. Persons in this group should have a serum sample tested for rabies antibody every 2 years; if the titer is less than complete neutralization at a 1:5 serum dilution by the RFFIT, the person also should receive a single booster dose of vaccine. Veterinarians, veterinary students, and animal-control and wildlife officers working in areas with low rabies rates (infrequent exposure group), and at-risk international travelers do not require routine preexposure booster doses of vaccine after completion of primary preexposure vaccination.

Post-exposure Therapy for Previously Vaccinated Persons

If exposed to rabies, previously vaccinated persons should receive two IM doses (1.0 mL each) of vaccine, one immediately and one 3 days later. Previously vaccinated persons are those who have received one of the recommended preexposure or postexposure regimens of HDCV, RVA, or PCEC, or those who received another vaccine and had a documented rabies antibody titer. RIG is unnecessary and should not be administered to these persons because an anamnestic response will follow the administration of a booster regardless of the prebooster antibody titer.

Preexposure Vaccination and Serologic Testing
Because the antibody response has been satisfactory after these recommended preexposure prophylaxis vaccine regimens, routine serologic testing to confirm seroconversion is not necessary except for persons suspected of being immunosuppressed. Patients who are immunosuppressed by disease or medications should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated. When that is not possible, immunosuppressed persons who are at risk for exposure to rabies should be vaccinated and their antibody titers checked. In these cases, failures to seroconvert after the third dose should be managed in consultation with appropriate public health officials.

Decision for Post-exposure Prophylaxis

Rationale for Treatment
Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency. Physicians should evaluate each possible exposure to rabies and, if necessary, consult with the Infectious Disease Epidemiology section regarding the need for rabies prophylaxis. The following factors should be considered before specific antirabies postexposure prophylaxis is initiated.

Type of Exposure:

Rabies is transmitted only when the virus is introduced into bite wounds or open cuts in skin or onto mucous membranes. If no exposure has occurred (i.e., no bite or nonbite exposure), postexposure prophylaxis is not necessary. The likelihood of rabies infection varies with the nature and extent of exposure.

- Bite: Any penetration of the skin by teeth constitutes a bite exposure. All bites, regardless of location, represent a potential risk of rabies transmission. Bites by some animals, such as bats, can inflict minor injury and thus be undetected.

- Nonbite: Nonbite exposures from terrestrial animals rarely cause rabies. However, occasional reports of transmission by nonbite exposure suggest that such exposures constitute sufficient reason to consider postexposure prophylaxis.

Animal source:

Dog, cat, or ferret:
A healthy domestic that bites a person may be confined and observed for ten days. Any illness in the animal during confinement or before release should be evaluated by a veterinarian and reported immediately to the local public health department. If signs suggestive of rabies develop, the animal should be euthanized and its head removed and shipped, under refrigeration, for examination by a qualified laboratory. If the biting animal is stray or unwanted, it should either be observed for ten days or be euthanized immediately and submitted for rabies examination.

- Raccoons, skunks, foxes, and coyotes are the terrestrial animals most often infected with rabies. All bites by such wildlife must be considered possible exposures to the rabies virus. Postexposure prophylaxis should be initiated as soon as possible after patients are exposed to wildlife unless the animal has already

been tested and shown not to be rabid. If postexposure prophylaxis has been initiated and subsequent immunofluorescence testing shows that the exposing animal was not rabid, postexposure prophylaxis can be discontinued. Signs of rabies among wildlife cannot be interpreted reliably; therefore, any such animal that exposes a person should be euthanized at once (without unnecessary damage to the head), and the brain should be submitted for rabies testing. If the results of testing are negative by immunofluorescence, the saliva can be assumed to contain no virus and the person bitten does not require postexposure prophylaxis.

- Bat exposure: Rabies postexposure prophylaxis is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. Postexposure prophylaxis might be appropriate even if a bite, scratch, or mucous membrane exposure is not apparent when there is reasonable probability that such exposure might have occurred. On the basis of the available but sometimes conflicting information from the 21 bat-associated cases of human rabies reported since 1980, in one to two cases, a bite was reported; in ten to twelve cases, apparent contact occurred but no bite was detected; in seven to ten cases, no exposure to bats was reported, but an undetected or unreported bat bite remains the most plausible hypothesis. Clustering of bat-associated human cases within the same household has never been reported. Consequently, postexposure prophylaxis should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite, scratch, or mucous membrane exposure did not occur. In instances in which a bat is found indoors and there is no history of bat-human contact, the likely effectiveness of postexposure prophylaxis must be balanced against the low risk such exposures appear to present. In this setting, postexposure prophylaxis can be considered for persons who were in the same room as the bat and who might be unaware that a bite or direct contact had occurred (e.g., a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person), and rabies cannot be ruled out by testing the bat. Postexposure prophylaxis would not be warranted for other household members.

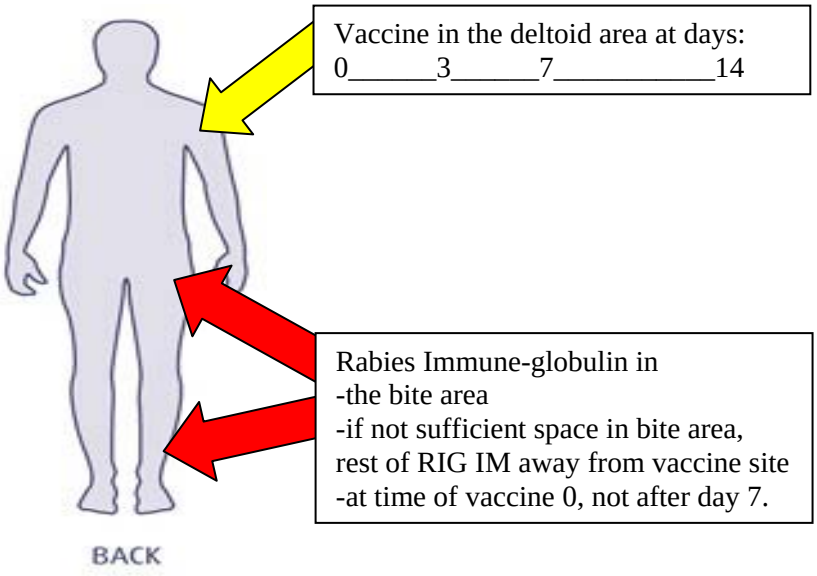
- Other Wild Animals: Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats and mice), and lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and have not been known to transmit rabies to humans. From 1990 through 1996, in areas of the country where raccoon rabies was enzootic, woodchucks accounted for 93% of the 371 cases of rabies among rodents reported to CDC. In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate antirabies postexposure prophylaxis. The offspring of wild animals crossbred to domestic dogs and cats (wild animal hybrids) are considered wild animals by the National Association of State and Public Health Veterinarians (NASPHV), and the Council of State and Territorial Epidemiologists (CSTE). Because the period of rabies virus shedding in these animals is unknown, these animals should be euthanized and tested rather than confined and observed when they bite humans. Wild animals and wild animal hybrids should not be kept as pets. Animals maintained in United States Department of Agriculture- licensed research facilities or accredited zoological parks should be evaluated on a case-by-case basis.

<u>Circumstances of Biting Incident and Vaccination Status of Exposing Animal</u>
An unprovoked attack by an animal is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. A currently vaccinated dog, cat, or ferret is unlikely to become infected with rabies.

Post-exposure prophylaxis

Postexposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have previously received complete vaccination regimens (preexposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers. These persons should receive only vac-

cine (see Postexposure Therapy for Previously Vaccinated Persons). The combination of RIG and vaccine is recommended for both bite and nonbite exposures, regardless of the interval between exposure and initiation of treatment.



Rabies Immune Globulin Use**.** RIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate antibodies until the patient responds to HDCV, RVA, or PCEC by actively producing antibodies. If RIG was not administered when vaccination was begun, it can be administered through the seventh day after the administration of the first dose of vaccine. Beyond the seventh day, RIG is not indicated since an antibody response to cell culture vaccine is presumed to have occurred. Because RIG can partially suppress active production of antibody, no more than the recommended dose should be administered. The recommended dose of human RIG is 20 IU/kg body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. This change in the recommendations for RIG administration is based on reports of rare failures of postexposure prophylaxis when smaller amounts of RIG were infiltrated at the exposure sites. RIG should never be administered in the same syringe or in the same anatomical site as vaccine.

Vaccine Use**.** Three rabies vaccines are currently available in the United States. Any one of the three can be administered in conjunction with RIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV, RVA, or PCEC should be administered intramuscularly. The first dose of the 4-dose course should be administered as soon as possible after exposure. Additional doses should be administered on days 3, 7, and 14, after the first vaccination. The fifth dose at day 28 is no longer recommended. Studies indicated that four vaccine doses in combination with rabies immune globulin (RIG) elicited adequate immune responses and that a fifth dose of vaccine did not contribute to more favorable outcomes.

For adults, the vaccination should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV, RVA, or PCEC injections because administration of HDCV in this area results in lower neutralizing antibody titers.

Vaccination And Serologic Testing

Serum samples from patients completing preexposure or postexposure prophylaxis do not need to be tested to document seroconversion unless the person is immunosuppressed. When postexposure prophy-

laxis has been properly administered, no treatment failures have occurred in the United States.

Although antibody levels do not define a person's immune status, they are a marker of continuing immune response. To ensure the continuity of an immune response, titers should be checked periodically, with booster doses administered as needed. Two years after primary preexposure vaccination, a 1:5 serum dilution will neutralize challenge virus completely (by the RFFIT) among 93% to 98% of persons who received the three-dose preexposure series intramuscularly and 83% to 95% of persons who received the three-dose series intradermally. If the titer falls below the minimum acceptable antibody level, a preexposure booster dose of vaccine is recommended for a person at continuous or frequent risk for exposure to rabies. The following guidelines are recommended for determining when serum testing should be performed after primary preexposure vaccination:

- A person in the continuous-risk category should have a serum sample tested for rabies antibody every six months.
- A person in the frequent-risk category should have a serum sample tested for rabies antibody every two years.

Adverse Reactions HDCV, RVA and PCEC

Reactions after vaccination with HDCV, RVA, and PCEC are less serious and less common than with previously available vaccines. In previous studies with HDCV, local reactions (e.g., pain, erythema and swelling or itching at the injection site) have been reported among 30% to74% of recipients. Systemic reactions (e.g., headache, nausea, abdominal pain, muscle aches and dizziness) have been reported among 5% to 40% of recipients. Three cases of neurologic illness resembling Guillain-Barre syndrome that resolved without sequelae in 12 weeks have been reported. In addition, other central and peripheral nervous system disorders have been temporally associated with HDCV vaccine, but a causal relationship has not been established in these rare reports.

An immune complex-like reaction occurred among approximately 6% of persons who received booster doses of HDCV two to 21 days after administration of the booster dose. The patients developed generalized urticaria, sometimes accompanied by arthralgia, arthritis, angioedema, nausea, vomiting, fever and malaise. In no cases have these reactions been life-threatening. This reaction occurred less frequently among persons receiving primary vaccination. The reactions have been associated with the presence of betapropiolactone-altered human albumin in the HDCV and the development of immunoglobulin E (IgE) antibodies to this allergen.

Rabies Immune Globulin (Human)

Local pain and low-grade fever might follow receipt of RIG. Although not reported specifically for RIG, angioneurotic edema, nephrotic syndrome and anaphylaxis have been reported after injection of immune globulin (IG), a product similar in biochemical composition but without antirabies activity. These reactions occur so rarely that a causal relationship between IG and these reactions has not been established.
Both formulations of RIG, BayRabTM and Imogam Rabies-HT, undergo multiple viral clearance procedures during preparation. There is no evidence that any viruses have ever been transmitted by commercially available RIG in the United States.

Head removal

Euthanasia should be accomplished in such a way as to maintain the integrity of the brain so that the laboratory can recognize the anatomical parts. Except in the case of very small animals (e.g., bats), only the head or brain (including brain stem) should be submitted to the laboratory.

Plastic or rubber gloves should be worn and care should be taken to avoid getting cut or getting the animal's body fluid in open cuts or sores. Make sure not to damage the head when killing the animal. **Do not shoot the animal in the head or smash the head.** Place specimen in a plastic bag and seal. Ideally, the head should be shipped in a styrofoam container with freeze packs to keep cool. **Do not use dry ice. Do not freeze**. The use of wet ice is acceptable only if the package containing the head will remain sealed. It is of utmost importance that the head be chilled immediately since it will rapidly deteriorate at room temperature and be unsuitable for laboratory testing. An animal head that is unable to be shipped by Friday may be kept refrigerated over the weekend, if necessary; however, because of the nature of the disease and the urgency for the test results, every effort should be made to submit the specimen as quickly as possible

Quarantine

Encourage the use of rabies vaccine in all domestic cats and dogs and in persons who handle animals on a regular basis (such as animal control personnel and staff in veterinarians' offices).

Educate the public, especially children, on avoiding contact with stray domestic or wild animals.

Prevention of Transmission

Animal Vaccination: Recommendations are discussed in the most recent Compendium of Animal Rabies Prevention and Control (*http://www.dhh.louisiana.gov/offices/page.asp?id=249&detail=7488*), listed below.

Hospital precaution and isolation:

The case would be hospitalized and standard precautions. Care should be taken by attending personnel to prevent saliva contact with open wounds and mucous membranes.

Dog exposure to a rabid or potentially rabid animal

If a dog was exposed to a known rabid animal (usually a bat), the dog should be euthanized or quarantined for six months with a vaccine given to the dog at five months.

If a dog was exposed to an animal whose rabies status is unknown, the dog should be immediately vaccinated against rabies, confined for 90 days and given booster vaccinations at day 21 (third week), and at day 56 (eighth week).

Infectious Disease Epidemiology Section
Office of Public Health, Louisiana Dept of Health & Hospitals
800-256-2748 (24 hr number) – (504) 219-4563
www.infectiousdisease.dhh.louisiana.gov

CANINE/FELINE RABIES CASE REPORT

Refer to the control of communicable disease manual for Specific information needed or contact the infectious disease epidemiology Section.

Reported by (Name)	Date of Report
JobTitle	Employer
Date of bite	Location
Humans exposed: []Y []N []Unknown	Kind of exposure; []Bite, []Scratch, []Other
Names, addresses and phone numbers of exposed	
Attack: []Provoked, []Unprovoked	
Circumstances	
Vaccine /RIG administered []Y []N []Unknown	
Other animals bitten: []Y []N []Unknown; describe	
Animal []Dog, []Cat, []Ferret, Skunk, []R[]Y []N []Unknown raccoon []Other:	[]Owned, always indoors, []Owned outside []Stray, []Wildlife
Exposed other rabid animal []Y []N []Unknown	[]In custody, []Ran away, []Dead
Disposition of animal in custody: []Ten day custody, []Sacrificed	
Describe clinical signs observed: []None or describe	
If dog, cat or ferret: vaccinated []Y []N []Unknown	
Type of vaccine	Date of vaccination
Name of veterinarian	Phone