Rabies Backgrounder

(October 27, 2009)

Causative agent

Rabies is caused by the rabies virus, an enveloped, bullet-shaped virus containing a single stranded, negative sense RNA molecule.[1] The rabies virus belongs to the *Lyssavirus* genus, a group of morphologically similar, antigenically and genetically related viruses in the Rhabdoviridae family. Other *Lyssaviruses* include Lagos bat virus, Mokola virus, Duvenhage virus, European bat *Lyssavirus* 1, European bat *Lyssavirus* 2, and Australian bat *Lyssavirus* (ABLV).

Numerous variants, or genetically distinct strains, of the rabies virus exist. These variants are named based on the species in which the variant was originally identified and, as applicable, the geographic location in which it was originally detected. Distinct rabies virus variants have been identified in different bat species; therefore, bat rabies variants are usually associated with the species of bat with which it was first associated. As of 2005, there are between 15 and 40 species of bats that may each have their own rabies virus variant.[2,3]

Examples of terrestrial (land animal) rabies variants in the United States include raccoon variants, skunk variants, mongoose variant (in Puerto Rico), arctic fox variant, red fox variant and gray fox variant. Genetically different rabies virus variants have also been identified in geographically separate populations of animals of the same species (e.g., gray foxes in Arizona and Texas and skunks in California, north central U.S. and south central U.S.). [4] A novel rabies virus variant associated with free-tailed bats was identified in 2008 following the death of a Mexican immigrant exposed to bats prior to her arrival in the U.S.[4]

Background

Rabies may be the oldest recognized infectious disease, and quite possibly the first recognized zoonotic disease. The first historical description of rabies dates from the 23rd century BC in the legal Eshuma Code of Babylon, relating to dog bites of humans. The word *rabies* has its origin in Sanskrit, 3000 years BBC: "rabhas" means "to do violence". The Greek word for *rabies*, "lyssa," derives from the root "lud" which means "violent". Thus, the genus of viruses to which rabies belongs is *lyssa*.[5]

Dogs are still the primary rabies reservoirs in developing countries. However, in North America, >90% of rabies cases in animals occur in wildlife.[4] The epizootiology (epidemiology) of the disease differs from one region or country to another and warrants the medical evaluation of all mammal bites.

Susceptibility and natural distribution

There are over 4,000 mammalian species which are susceptible to rabies, although only a few of these species are considered major reservoir hosts. Worldwide, the primary reservoirs are carnivores and bats. As it pertains to rabies, the term "reservoir species" refers to the circulation of the rabies virus within a wildlife species; virus transmission is primarily between members of the same species (sylvatic circulation). However, affected individuals of these species that become clinically affected by rabies and are also capable of transmitting the virus to different species

(spillover infection). In the United States, the most common reservoir species are raccoons, bats, skunks and foxes.[4]

Rabies risk and veterinarians

Rabies exposure is an inherent risk associated with the practice of veterinary medicine.[6] Veterinarians may be exposed to the rabies virus by examination, animal bite pr scratch, or necropsy of infected animals. According to the National Association of State Public Health Veterinarians (NASPHV) Compendium of Veterinary Standard Precautions for Zoonotic Disease Prevention in Veterinary Personnel,[7]

> ***Necropsy is a high-risk procedure because of potential contact with infectious agents in body fluids and aerosols and on contaminated sharps. Nonessential persons should not be present during necropsy procedures. Veterinary personnel should wear gloves, facial protection, and impermeable protective outerwear as needed. In addition, cut-proof gloves should be used to prevent sharps-associated injuries. Respiratory tract protection and environmental controls should be employed when band saws or other power equipment are used.***

Veterinary personnel who have contact with animals should be offered pre-exposure vaccination in accordance with recommendations of the Advisory Committee on Immunization Practices (ACIP). Bat rehabilitators should also consider pre-exposure vaccination.[2]

Worldwide

According to the World Health Organization (WHO), rabies is widely distributed across the globe and is found on all continents except Antarctica. In certain areas of the world, canine rabies remains an established source of human rabies infection, including (but not limited to) parts of Africa, Asia, and Central and South America.

More than 55,000 people die of rabies each year – 95% of them in Africa and Asia. The majority of human deaths in these areas occur as a result of a bite from an infected dog. Asia has the highest number of human rabies cases annually, accounting for more than 80% of human cases worldwide. Human rabies cases have dramatically increased in China in the last decade, reaching a new peak in 2007.[8,9] High dog population density, lack of proper vaccination and a lack of national systemic surveillance for rabies have contributed to the continual re-emergence of rabies in China.[8]

United States

As in most developed countries, wild animals account for the majority of all rabies cases; 93% of the cases reported to the CDC during 2008 were wild animals, and the remaining 7% of cases were domestic animals.[4] The most frequently reported rabid wildlife species remain raccoons, bats, skunks, and foxes; however, their relative proportions have continued to fluctuate because of epizootics of rabies among animals infected with several distinct rabies virus variants.[4] Other rabies cases reported in 2008 included mongoose, groundhogs, bobcats, coyotes, white-tailed deer, opossums, rabbits, a beaver, a coati , a cougar, and a river otter.[4]

In the U.S., most cases of rabies in humans result from infection with bat rabies variants.[4] According to the U.S. Geological Survey National Wildlife Health Center, 1 in 10 disabled bats submitted for rabies testing in the U.S. tests positive for rabies.[2] However, the majority (86%) of post-exposure rabies prophylaxis (PEP) in humans is administered due to exposure to rabid or potentially rabid dogs and cats.[4,10]

The raccoon rabies variant has become the predominant rabies variant in all of the eastern U.S. coastal states as well as Alabama, Ohio, Pennsylvania, Tennessee, Vermont and West Virginia.[4]

Cats may be more likely to contract rabies than dogs because cats are less likely to be vaccinated for rabies and are more likely to roam outside unsupervised. In 2008, the number of rabies-infected cats was almost 4 times the number of rabies-infected dogs and 5 times the number of rabies-infected cattle.[4] In Maryland, approximately 194 persons received post-exposure prophylaxis (PEP) during 1983-1986 because of rabid cat exposures.[11] In 1994 in New Hampshire, approximately 600 persons received PEP after exposure to a single rabid cat.[12] Between 1995 and 2000, exposure to rabid cats accounted for 24% of 2,216 exposures requiring PEP in upstate New York.[13]

Extensive rabies vaccination campaigns in the 1940s and 1950s resulted in a substantial decline of rabies in domestic animals and also eliminated the circulation of a major canine rabies variant in dogs by the late 1960s. During the late 1980s in southern Texas, a canine rabies variant associated with coyotes had begun to emerge in unvaccinated dogs in southern Texas. Oral vaccination programs were initiated, and no cases of animals infected with the coyote rabies virus variant have been reported since 2004; this variant is considered eliminated from the U.S. Another canine rabies virus associated with grey foxes in western and central Texas has similarly been eliminated, and the US was declared free of canine variant rabies in 2007.[14]

Importation of rabid dogs poses a risk of reintroduction of the canine rabies variant. A rabid puppy was imported from India in 2007, and a rabid dog was imported from Iraq into New Jersey in 2008.[4,15] Since 2004, at least 4 cases of rabies in recently imported dogs have been reported,[4] emphasizing the need for continued surveillance and preventive measures.

Stray animals continue to pose a risk of rabies to humans. In 2007, an apparently healthy, stray kitten was handled by players on several girls' softball teams during a multi-state tournament in South Carolina. The kitten exhibited signs of illness shortly afterward, and tested positive for the eastern raccoon variant of rabies. An extensive public health investigation identified 27 persons in 3 states with exposure necessitating PEP.[16]

Transmission

The rabies virus is secreted in saliva, and is usually transmitted by a bite from an infected animal. It also can be transmitted when the saliva from an infected mammal comes in contact with open wounds or mucous membranes (eg, eye, nose or mouth). The virus is excreted in the saliva of infected terrestrial animals during clinical illness and for only a few days prior to illness or death. Bats can transmit the virus by bite as early as 12 days before clinical signs appear and 24 days before the bat's death.[2]

Rarely, cases of rabies infection of humans have occurred following inhalation of the virus in bat-infested caves and corneal or organ transplantation from an infected donor.[17,18,19] Personnel that work with rabies, either in a laboratory or biologic production setting, are considered at-risk for inhalation or contact exposure to the virus.[7,20]

Rabies is not transmitted via contact with blood, urine, or feces of an infected animal. Tissues and products from a rabid animal should not be used for human or animal consumption.[7] Because the pasteurization process kills the rabies virus, inadvertent consumption of pasteurized milk obtained from a rabid cow does not constitute rabies exposure.[7] Transmission of rabies through unpasteurized milk has not been documented, but is theoretically possible.[21]

Pathology, incubation periods and clinical signs

Pathology

Once introduced into a new mammalian host by a bite or by salivary contamination of an open wound, the virus multiplies in the wound site and invades the sensory neurons. It then travels via the nerve cell axons to the central nervous system. The affected individual develops encephalitis

(inflammation of the brain), and the nerve cells of the brain exhibit demyelination (loss of myelin, a protecting and insulating layer in the sheath surrounding the neuron's axon) and death. Eosinophilic cytoplasmic inclusions, termed Negri bodies, are characteristic of rabies virus infection.[1]

Incubation periods

Rabies incubation periods in bats can last from 21 days to more than 209 days. The incubation periods in mammals vary widely depending on the site of the bite and the amount of virus introduced with the exposure. Because the virus travels along nerves to the central nervous system,[1] introduction of the virus in areas farther from the central nervous system (such as the hands or feet) results in longer incubation times because the virus must travel a longer distance before it reaches the central nervous system.[22]

Incubation periods in animals can range from 2 weeks to many months. The average incubation period in cats and dogs is 2 months, but it can range from 2 weeks or several months or even years.[23] In humans, incubation periods can range from 5 days to more than one year, with an average of 1-3 months.[24]

Clinical signs in animals

Visible wounds may be the first observed indication of potential exposure to rabies. Rabies is often classified as paralytic (dumb) rabies or encephalitic (furious) rabies based on the clinical signs observed.[2,24] Encephalitic rabies is characterized by aggression and brain disorders, whereas paralytic rabies is characterized by depression and worsening paralysis. However, the observed clinical signs can vary with each form and animals may transition from one form to the other during the course of the disease.[25]

The first clinical signs of rabies in animals are usually nonspecific and may include lethargy, vomiting, fever, and anorexia (loss of appetite). Signs rapidly progress and in days may include restlessness, confusion/disorientation, ataxia/incoordination, lameness, hypersalivation, weakness, paralysis, aggression, self mutilation, tremors, seizures, choking, or difficulty breathing or swallowing. Rabid cats are more likely to exhibit aggressive behavior (encephalitic rabies), whereas rabid dogs are more likely to exhibit lethargy and paralysis (paralytic rabies).[10] Death usually occurs within 1-10 days of the appearance of clinical signs.[1,23]

Experimentally infected horses initially exhibited muzzle tremors, followed by pharyngeal (throat) dysfunction (spasm or paresis), ataxia, weakness, lethargy and dullness. Approximately 43% of the rabid horses displayed encephalitic rabies; some of these animals initially displayed paralytic rabies. The incubation period in experimentally infected horses averaged 12.3 days, and death occurred at an average of 5.5 days.[26]

Experimentally infected cattle and sheep exhibited average incubation periods of 15.1 and 10.0 days, respectively. Death occurred at an average of 3.7 and 3.25 days, respectively. The clinical signs observed in rabid cattle included excessive salivation, behavioral changes, muzzle tremors, increased bellowing, aggression, increased skin sensitivity, increased excitability and pharyngeal (throat) dysfunction. Sheep exhibited muzzle and/or head tremors, aggression, increased excitability, increased skin sensitivity, trismus (lockjaw), excessive salivation, excessive bleating and recumbency. Approximately 70% of cattle and 80% of sheep experimentally infected with the rabies virus developed the encephalitic form of rabies.[27]

Rabid bats more often display paralytic rabies, but unprovoked attacks and aggression can be observed.[2] Lethargic bats or those that appear unable to fly may be rabid or may simply be injured.[2] Rabid bats may also die in their shelters.[2]

Diagnosis

Rabies testing should be performed in accordance with the CDC standardized protocol.[28] The testing should be performed by a qualified laboratory as designated by state or local health authorities.

The most commonly used test to diagnose rabies in animals is the direct fluorescent antibody test (dFA).

- This is a post-mortem test, as it requires brain tissue from the suspected animal, and the brain should be left intact.
- It is highly recommended that the head of the animal be refrigerated (not frozen) when shipped to the diagnostic laboratory.
- Chemical fixation of brain tissue should be avoided. Except for the submission of very small animals (e.g., bats), only the head or brain (including brain stem) should be shipped.[7]

Blood tests (serology) can not reliably determine the status of infection or immunity and serologic testing can not be used in lieu of the dFA test.

Treatment and management of exposed animals

According to the Compendium of Animal Rabies Prevention and Control,[7] immediate cleansing of the wound, followed by immunization (in previously immunized animals) with a USDA-approved rabies vaccine as soon as possible after any suspected contact with a rabid animal, can prevent the onset of rabies in almost 100% of exposures.

The following scenarios present the current recommendations for management of exposed animals as determined by the NASPHV. Please note that states and local municipalities may have established regulations regarding the disposition of exposed animals that may differ from these recommendations. Veterinarians are urged to contact their local animal control offices regarding the laws governing their locality.

Scenario 1: A vaccinated animal is bitten by a potentially or known rabid animal

- Pets (dogs, cats, ferrets)

  If currently vaccinated, these pets should be re-vaccinated immediately, and watched closely by their owner for any clinical signs of illness for 45 days. The owner should report any signs of illness immediately to their veterinarian, and the veterinarian should report any suspect case immediately to the local health department. If signs suggestive of rabies develop, the animal should be immediately euthanatized and the head shipped for testing.

  Pets overdue for booster vaccinations at the time of exposure should be evaluated on a case-by-case basis, based on the severity of the exposure, the number of prior vaccinations, time elapsed since the last vaccination, the animal's current health status, and the local area's rabies variants and epidemiology. If signs suggestive of rabies develop, the animal should be immediately euthanatized and the head shipped for testing.

- Livestock

  Livestock exposed to a rabid animal and currently vaccinated with a USDA-approved vaccine labeled for use in that species should be revaccinated immediately and observed

by the owner for 45 days. The owner should report any signs of illness immediately to their veterinarian, and the veterinarian should report any suspect case immediately to the local health department. If signs suggestive of rabies develop, the animal should be immediately euthanatized and the head shipped for testing.

Handling and consumption of tissues from exposed animals may carry a risk for rabies transmission and infection. If an exposed but clinically normal animal is to be slaughtered for consumption, it should be done immediately after exposure. All personnel handling the animal, its tissues or its carcass should use barrier protection, and all tissues of the animal should be thoroughly cooked before consumption. Federal guidelines for meat inspectors require that any animal known to have been exposed to rabies within 8 months be rejected for slaughter. USDA Food and Inspection Service (USDA-FSIS) meat inspectors should be notified if such exposures occur in food animals before slaughter.

- Animals maintained in licensed research facilities or in accredited zoological parks should be evaluated on a case-by-case basis.

Scenario 2: A non-vaccinated animal is bitten by a potentially or known rabid animal

- There are currently no USDA-licensed biologics for postexposure rabies prophylaxis of unvaccinated animals. The exposed animal should be euthanatized immediately. If the owner is not willing to euthanatize the animal, the animal must be kept in strict isolation, in an enclosure and with no direct contact with humans or other animals, for 6 months. If signs suggestive of rabies develop, the animal should be immediately euthanatized and the head shipped for testing.[7]

Guidelines for pre-exposure and post-exposure rabies prophylaxis for humans as determined by the Advisory Committee on Immunization Practices (ACIP) can be found at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e507a1.htm

Prevention and Control

Vaccination of owned animals

The National Association of State Public Health Veterinarians, Inc (NASPHV) recommends that local governments should initiate and maintain programs to ensure rabies vaccinations for all pet dogs, cats and ferrets; and that strays and unwanted animals should be removed, and any adopted animals are vaccinated.[7]

NASPHV guidelines recommend initial vaccination for rabies no earlier than 12 weeks of age, a booster vaccination 1 year after the initial vaccination, and additional, regular booster vaccinations as directed by the vaccine manufacturer. Microchip implantation of pets is highly recommended to facilitate identification and determination of rabies vaccination status if the animal bites another animal or a person.

Peak rabies antibody titers are reached 28 days after the initial rabies vaccination, and the animal is considered immunized at that time.[7] According to the NASPHV, an animal is considered "currently vaccinated" and immunized if the initial vaccine was administered at least 28 days prior to exposure or booster vaccinations have been administered according to guidelines.

Due to the public health significance of rabies, rabies vaccines should be administered by or under the direct supervision of a licensed veterinarian. A licensed veterinarian should always

examine a healthy dog, cat, or ferret that is vaccinated against rabies and reportedly bites a human. If no signs of illness compatible with rabies are detected, the animal should be quarantined under conditions outlined in an official quarantine order issued by the rabies control authority or a public health official and observed for 10 days from the date of the bite, otherwise the animal can be euthanatized in an approved laboratory for testing.

Although vaccination remains a critically valuable tool in the prevention of rabies, vaccination is not 100% effective. Rabies is extremely uncommon in vaccinated dogs and cats, but does occur. Murray et al determined that 35 (3.2%) of 1,104 rabid dogs and cats had a history of rabies vaccination.[10] Two of the 13 rabid dogs with a history of vaccination were considered "currently vaccinated" according to NASPHV guidelines, 5 were classified as not currently vaccinated, 4 were within 28 days of the first vaccine dose administration at the time of rabies onset, and vaccination status was unknown or could not be classified for the remaining 2 dogs. Similarly, 3 of 22 rabid cats were considered currently vaccinated, 8 were not currently vaccinated, 6 were within 28 days of first vaccination, and 5 cats had unknown or unclassified vaccination status. Two dogs and 3 cats had been administered booster doses of rabies vaccine after exposure to a rabid animal. Reasons for vaccine failure in these animals were unknown, but possible explanations include use of improperly stored or expired vaccines; failure of the animal to mount an appropriate immune response due to immunocompromise, immunosuppressive disease or corticosteroid treatment; or exposure to a particularly virulent rabies virus variant.

Other preventive measures for pet owners

Roaming pets are at increased risk of contact with potentially rabid wildlife; therefore, owners should not let their pets roam free. Spayed and neutered pets may be less likely to roam.

Adults should instruct children never to handle or approach unfamiliar animals, particularly wildlife including feral cats, regardless of how friendly the animal appears to be. Wounded or dead unfamiliar animals should never be handled, and local animal control authorities should be contacted for safe removal of the animal.

International importation of dogs and cats

Importation of dogs and cats into the U.S. is regulated by the Centers for Disease Control and Prevention (CDC), and is subject to vaccine requirements as stated in the Federal Code (42 CFR, Part 71.51). Basic information regarding animal importation into the U.S. can be found at the CDC's page, "Bringing an animal into the United States". Dogs not accompanied by proof of vaccination, or those too young for vaccination prior to importation, are permitted only if a confinement agreement is signed and the animal is confined by the importer as instructed.

Livestock/Horses

Valuable livestock and horses and any other animals that have frequent contact with humans should be vaccinated against rabies.

Some "rabies-free" areas may require evidence of vaccination and the presence of rabies virus antibodies, via antibody titers, before allowing importation of animals.[7]

Wildlife

The control of rabies in wildlife is difficult. Vaccination of free-ranging wildlife or selective population reduction may be successful in certain situations, but it depends on each rabies outbreak. Distribution of oral vaccinia-rabies glycoprotein recombinant vaccines has shown preliminary success in controlling rabies in raccoons in the eastern states and coyotes and foxes in Texas.[4,29] Because of the risk of rabies in wild animals (especially raccoons, skunks, coyotes, foxes, and bats), the American Veterinary Medical Association (AVMA) and the National Association of State Public

Health Veterinarians (NASPHV) strongly encourage state laws prohibiting the importation, distribution, translocation, and private ownership of wildlife.

Wild animals should never be kept as pets due to the risk of injury, rabies and other zoonotic diseases. Other commonsense measures can be taken to minimize human contact with potentially rabid wild animals, including:

- Avoid leaving exposed garbage or pet food outside, as it may attract either wild animals or roaming pets.
- Wild animals should be observed from a distance, and never should be fed or handled.
- If a person sees any wild or stray animal acting strangely, they should immediately report it to city or county animal control personnel.

Zoo animals

Captive mammals are potentially at risk of coming into contact with a rabid animal. There is also the risk that a new wild animal sent to the zoo may be in the incubation stage of rabies infection when captured; therefore, a 6-month quarantine is recommended before introducing any new animal into the zoo population. The use of pre- or post-exposure vaccinations for zoo handlers who may have been exposed to a rabid animal may reduce the need for euthanasia of other captive animals. Bats and carnivores should always be housed so that they are prevented from direct contact with the public.[7]

Morbidity and Mortality

Once an animal exhibits clinical signs of rabies, the disease is 100% fatal. Although a small number of humans have recovered from symptomatic rabies infection, the disease is almost 100% fatal in humans once symptoms appear.

Early intervention, in the form of wound management and post-exposure prophylaxis as indicated, has a high success rate in preventing rabies infection in humans.

We would like to thank the AVMA Council on Public Health and Regulatory Veterinary Medicine (CPHRVM), the AVMA Council on Biologic and Therapeutic Agents (COBTA), and the AVMA Clinical Practitioners Advisory Committee (CPAC) for their assistance in reviewing this document.

Links to more information about rabies

AVMA

AVMA Policy: Rabies
AVMA World Rabies Day landing page
What you should know about rabies client information brochure
What you should know about dog bite prevention client information brochure
Zoonosis update: Rabies
Dog Bite Prevention Interview with Dr. Gregory S. Hammer
Does Your Pet Need a Rabies Shot? (Spanish Language)

Rabies Surveillance in the United States manuscripts, as published in the *Journal of the American Veterinary Medical Association*
2008
2007
2006
2005

2004
2003
2002
2001
2000
1999

World Rabies Day official site

Centers for Disease Control and Prevention (CDC)
Rabies
Information for Veterinarians
Advisory Committee on Immunization Practices (ACIP)
Bringing an animal into the United States
Podcasts:
- Rabies Elimination in Dogs in the United States
- Stray Kitten, Scary Problem
- Rabies and Risk to Travelers

National Association of State Public Health Veterinarians
Compendium of Animal Rabies Prevention and Control

US Department of the Interior – US Geological Survey (USGS)
Bat rabies and other Lyssavirus infections

World Health Organization (WHO)
Rabies

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