Rabies

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Importance

Rabies is a neurological disease of mammals that is almost invariably fatal once the clinical signs develop. Humans are usually infected when they are bitten by an infected animal, or exposed to its saliva or central nervous system (CNS) tissues. Although rabies is generally well controlled among domesticated animals in developed nations, canine rabies continues to be a serious problem in some areas of Africa, the Middle East, Asia and Latin America. Wildlife reservoirs have become increasingly important where canine rabies is under control. Rabies can be effectively treated if the exposure is recognized before the symptoms develop. However, people in impoverished countries do not always have access to post-exposure prophylaxis, and even in nations with good medical care, cases occur occasionally in people who do not realize they were exposed.

Etiology

Rabies results from infection by the rabies virus, a neurotropic virus in the genus *Lyssavirus*, family Rhabdoviridae. It is classified as genotype 1, serotype 1 in this genus. There are many strains of the rabies virus; each strain is maintained in particular reservoir host(s). Although these viruses can readily cause rabies in other species, they usually die out during serial passage in species to which they are not adapted. The reservoir host is sometimes used as an adjective to describe a strain's origin. For example, if a virus from a skunk caused rabies in a dog, it would be described as skunk rabies in a dog, whereas a virus that is maintained in dog populations would be called canine rabies. Occasionally, a virus adapted to one species becomes established in another species. In the United States, skunk populations have been infected with raccoon and bat rabies variants, and canine rabies has become established in some populations of wild animals, such as gray foxes in Texas and Arizona.

Closely related lyssaviruses, which are known as rabies-related lyssaviruses or nonrabies lyssaviruses, can cause a neurological disease that is identical to rabies. Lagos bat virus (genotype 2, serotype 2) is found in bats in parts of Africa, and has caused fatal cases of neurological disease in cats, dogs and a water mongoose (*Atilax paludinosis*). Some of these cats and dogs had been vaccinated against rabies. Mokola virus (genotype 3, serotype 3) is the only rabies-related lyssavirus that has not been found in bats. This virus has been isolated from rodents and shrews in Africa, but its reservoir host is unknown. It has caused fatal neurological disease in cats, dogs and humans, including rabies-vaccinated cats and dogs. Antibodies to Mokola virus have been reported in some healthy animals, and one child who might have been infected with this virus recovered. Duvenhage virus (genotype 4, serotype 4) occurs among bats in Africa. It has caused fatal rabies-like disease in several people. The European bat lyssaviruses (EBLV) are very similar to the Duvenhage virus, but are found in continental Europe. They are serotype 5 and are subdivided into 2 biotypes, EBLV1 (genotype 5) and EBLV2 (genotype 6). Clinical cases have been reported in animals (sheep, a stone marten) and humans. The Australian bat lyssavirus (ABLV; genotype 7) has been isolated in Australia. It has also been reported from humans with fatal rabies-like disease.

Rabies and the rabies-related lyssaviruses have been classified into 2 phylogroups, based on how closely they are related. Phylogroup I contains the rabies virus, Duvenhage virus, EBLV1, EBLV2 and Australian bat virus, while phylogroup II consists of Lagos bat virus and Mokola virus. Four additional Eurasian bat viruses have also been tentatively classified as lyssaviruses. They include Irkut virus, Aravan virus and Khujand virus, which all belong to phylogroup I, and West Caucasian bat virus. Unless otherwise specified, the information in this outline refers to the classical rabies virus.

Geographic Distribution

With some exceptions (particularly islands), the rabies virus is found worldwide. Some countries including the United Kingdom, Ireland, Sweden, Norway, Iceland, Japan, Australia, New Zealand, Singapore, most of Malaysia, Papua New Guinea, the Pacific Islands and some islands in Indonesia have been free of the classical rabies

virus for many years. According to the World Health Organization (WHO), a country is considered to be free of rabies if there have been no indigenously acquired cases in humans or animals during the previous 2 years, in the presence of adequate surveillance and import regulations. Using this definition, several additional countries are considered to be free of rabies. In some cases, these nations have conducted rabies vaccination programs in wildlife, but are susceptible to the reintroduction of the virus from neighboring countries. Official lists should be consulted for the current list of rabies-free countries and areas, as it may change. For example, rabies was recently introduced into the island of Bali (Indonesia), which had been free of rabies for many years.

The presence of the rabies-related lyssaviruses does not prevent a nation from being listed as rabies-free. For example, European bat lyssaviruses have been isolated from bats and a human with neurologic disease in the United Kingdom. Other countries considered to be rabies-free, such as Australia, also contain rabies-related lyssaviruses. These viruses have not been reported from the Americas.

Transmission

The rabies virus is readily transmitted between mammals, whether they are the same or different species. This virus is usually spread in the saliva, when an infected animal bites another. Less often, an animal or person is infected by contact with infectious saliva or neurological tissues, through mucous membranes or breaks in the skin. The rabies virus is not transmitted through intact skin.

There are also rare reports of transmission by other routes. A few cases have been reported after transplantation of organs, particularly corneas but also pancreas, kidneys and liver. Aerosol transmission has been documented in special circumstances, such as in laboratories and bat caves with an unusually high density of aerosolized, viable virus particles. Rabies viruses have been transmitted by ingestion in experimentally infected animals, and there is anecdotal evidence of transmission in milk to a lamb and a human infant. (More conventional routes of spread could not be ruled out in the latter case.) There is some speculation that ingestion could play a role in rabies transmission among wild animals. One epizootic among kudu may have spread between animals when they fed on thorn trees. There are no records of human disease acquired by this route. Nevertheless, in 2 incidents investigated by the U.S. Centers for Disease Control and Prevention (CDC), people who drank unpasteurized milk from rabid cows were given post-exposure prophylaxis. Pasteurized milk and cooked meat are not expected to pose a risk of infection, as the rabies virus is inactivated by heat; however, as a precaution, the National Association of State Public Health Veterinarians recommends against consuming tissues and milk from rabid animals.

The dissemination of the rabies virus within the body

Immediately after infection, the rabies virus enters an eclipse phase during which it is not easily detected. During this phase, it replicates in non-nervous tissue such as muscle. It does not usually stimulate an immune response at this time, but it is susceptible to neutralization if antibodies are present. After several days or months, the virus enters the peripheral nerves and is transported to the central nervous system by retrograde flow in the axons. After dissemination within the CNS, where clinical signs develop as the neurons are infected, the virus is distributed to highly innervated tissues via the peripheral nerves. Most of the virus is found in nervous tissue, salivary glands, saliva and cerebrospinal fluid (CSF), which should all be handled with extreme caution.

Some virus has also been detected in other tissues and organs, including the lungs, adrenal glands, kidneys, bladder, heart, ovaries, testes, prostate, pancreas, intestinal tract, cornea, germinal cells of hair follicles in the skin, sebaceous glands, tongue papillae and the brown fat of bats. The rabies virus is contained within the neurons, and handling most body fluids or intact organs is thought to carry a low risk of infection. However, a puncture could theoretically pierce a neuron, and health care personnel are given post-exposure prophylaxis after a needlestick or other puncture wound received while caring for a rabies patient. Organ transplants also pose a (rare) risk, if the donor is not known to have been infected with rabies. Blood, urine and feces are not thought to be infectious; however, a few studies have suggested that viremia might occur at some point during the infection. A recent study in mice, using a polymerase chain reaction (PCR) assay, found viral RNA in mice when they were clinically ill, but not during the asymptomatic stage when virus was migrating to the CNS.

Epidemiological cycles

Rabies is maintained in two epidemiological cycles, one urban and one sylvatic. In the urban rabies cycle, dogs are the main reservoir host. This cycle predominates in areas of Africa, Asia, and Central and South America where the proportion of unvaccinated and semi-owned or stray dogs is high. It has been virtually eliminated in North America and Europe; although sporadic cases occur in dogs infected by wild animals, the urban cycle is not perpetuated in the canine population.

The sylvatic (or wildlife) cycle is the predominant cycle in Europe and North America. It is also present simultaneously with the urban cycle in some parts of the world. The epidemiology of this cycle is complex; factors affecting it include the virus strain, the behavior of the host species, ecology and environmental factors. In any ecosystem, often one and occasionally up to 3 wildlife species are responsible for perpetuating a particular strain of rabies. The disease pattern in wildlife can either be

relatively stable, or occur as a slow moving epidemic. Recent examples of epidemics include a fox rabies epidemic that moved slowly west in Europe, and a raccoon rabies epidemic that moved north along the east coast of the U.S. and into Canada.

Disinfection

The rabies virus can be inactivated by lipid solvents (soap solutions, ether, chloroform, acetone), 1% sodium hypochlorite, 2% glutaraldehyde, 45-75% ethanol, iodine preparations, quaternary ammonium compounds, formaldehyde or a low pH. This virus is also susceptible to ultraviolet radiation or heat of 1 hour at 50°C. It is rapidly inactivated in sunlight, and it does not survive for long periods in the environment except in a cool dark area.

Infections in Humans

Incubation Period

In humans, the incubation period is a few days to several years. Most cases become apparent after 1 to 3 months. In one study, approximately 4-10% of cases had an incubation period of 6 months or more.

Clinical Signs

The early symptoms may include nonspecific prodromal signs such as malaise, fever or headache, as well as discomfort, pain, pruritus or sensory alterations at the site of virus entry. After several days, anxiety, confusion and agitation may appear, and progress to insomnia, abnormal behavior, hypersensitivity to light and sound, delirium, hallucinations, slight or partial paralysis, hypersalivation, difficulty swallowing, pharyngeal spasms upon exposure to liquids, and convulsions. Either an encephalitic (furious) form with hyperexcitability, autonomic dysfunction and hydrophobia, or a paralytic (dumb) form characterized by generalized paralysis, may predominate. Death usually occurs within 2 to 10 days; survival is extremely rare.

Communicability

Human saliva contains the rabies virus; person-to-person transmission is theoretically possible but rare. Activities that could pose a risk for exposure include bites, kisses or other direct contact between saliva and mucous membranes or broken skin, sexual activity, and sharing eating or drinking utensils or cigarettes. It is not known how long humans can shed the virus before becoming symptomatic; the CDC recommends post-exposure prophylaxis for anyone who had at-risk contact with a person during the 14 days before the onset of clinical signs.

The CDC also recommends prophylactic treatment after a needlestick or other sharp object injury during an autopsy or during patient care, due to the possibility that the object could have passed through nervous tissue. Feces, blood, urine and other body fluids are not thought to carry the virus. A few cases of transmission have been reported in corneal transplants or transplanted internal organs.

Diagnostic Tests

Antemortem diagnosis may include the detection of antigens or nucleic acids, virus isolation or serology. RT-PCR or immunofluorescence may detect viral nucleic acids or antigens in saliva, or in skin biopsies taken from the nape of the neck. In skin, the virus occurs in the cutaneous nerves at the base of the hair follicles. Rabies virus is sometimes found in corneal impressions or eye wash fluid, and RT-PCR may occasionally detect nucleic acids in CSF. Virus isolation is helpful in either antemortem or postmortem diagnosis. Rabies virus can sometimes be isolated from the saliva, conjunctival secretions/tears, corneal impressions, skin biopsies or (less often) CSF in living patients, and from the brain at autopsy. Mouse neuroblastoma (MNA) cells and other cell lines can be used to recover the virus. Animal inoculation into weanling mice may also be done. More than one test is usually necessary for an antemortem diagnosis, as the virus is not invariably present in any tissue other than the CNS. Rabies is usually undetectable during the incubation period, and infections can also be difficult to diagnose when the clinical signs first appear. In some cases, rabies virus cannot be isolated even when antigens or nucleic acids are detected by other methods. Postmortem diagnosis is usually by immunofluorescence to detect viral antigens in the brain.

Serological tests include indirect immuno-fluorescence, virus neutralization and enzyme-linked immunosorbent assay (ELISA), and can be performed on serum or CSF. The detection of antibodies in the CSF is definitive; however, antibodies in the serum might also result from vaccination or the administration of human rabies immunoglobulin. Circulating neutralizing antibodies do not usually appear until late, and infected people may still be seronegative when they die.

Treatment

Postexposure prophylaxis consists of immediate wound cleansing and disinfection, followed by rabies vaccination and the administration of human rabies immunoglobulin. The rabies vaccine is given as 5 doses in the U.S., and it is usually administered intramuscularly in the arm. Fewer doses and no rabies immunoglobulin are given if the person was previously vaccinated. Postexposure prophylaxis is highly effective if it is begun soon after exposure.

There is no effective treatment once the symptoms develop. Vaccines, antiviral drugs such as ribavirin, interferon-alpha, passively administered anti-rabies virus antibodies (human immunoglobulin or monoclonal antibodies), ketamine and/or the induction of a coma have been tried in the past, but were usually ineffective.

Treatment is often palliative, and there is a very high probability of an unsuccessful outcome. One patient who recovered well was treated with ribavirin and supportive care including the induction of a therapeutic coma; however, the same treatment protocol has been unsuccessful in other patients. If treatment is successful in sustaining life, there may be permanent and possibly severe neurologic defects.

Prevention

Domesticated animals (especially dogs, cats and ferrets) should be vaccinated to prevent them from becoming infected and transmitting rabies to humans. Stray animals should also be controlled. Dogs, in particular, act as reservoirs for a canine variant of the rabies virus. Cats are readily infected by rabies, but a cat-specific variant does not occur in feline populations. Wild animals should not be handled or fed; wildlife behaving abnormally should particularly be avoided. Bats should be kept out of houses and public buildings. In some areas, wild animals are vaccinated orally, using baits.

Veterinarians and animal control officers should handle potentially rabid animals with extreme caution. Protective clothing such as thick rubber gloves, eye goggles and a plastic or rubber apron should be worn when doing autopsies or in other circumstances when exposure to infectious tissues could occur.

Bites or other exposures should be reported immediately. Post-exposure prophylaxis consists of immediate wound cleansing and disinfection, rabies vaccination and the administration of human rabies immunoglobulin. Asymptomatic dogs, cats or ferrets that have bitten humans are observed for 10 days; if the animal develops symptoms of rabies during this time, it is euthanized and tested for rabies.

An inactivated human vaccine is available for veterinarians, animal handlers, wildlife officers, laboratory workers and others at a high risk of exposure. International travelers may also be vaccinated in some cases. People who have been vaccinated must still receive post-exposure prophylaxis, but vaccination eliminates the requirement for rabies immunoglobulin and decreases the number of post-exposure vaccinations. It may also provide some protection for persons with inapparent exposure, or enhance immunity if postexposure prophylaxis is delayed. Rabies vaccines seem to provide some degree of cross-protection against rabies-related lyssaviruses in phylogroup I, but there is little or no cross-protection with the viruses in phylogroup II (Mokola virus and Lagos bat virus). The amount of protection against phylogroup I viruses may vary with the specific virus.

Morbidity and Mortality

In the U.S., clinical rabies is rare in humans, with 0-3 cases usually reported each year. Deaths are usually reported in people who did not realize they had been exposed or, for some other reason, did not seek medical treatment. Post-exposure prophylaxis, begun promptly, is almost always successful. Human rabies is also rare in Canada, most European countries, and some countries in South America. The prevalence rates are high in some parts of the developing world. Worldwide, over 90% of rabies cases occur after exposure to rabid dogs. In countries with a high percentage of vaccinated dogs, they are much less important as a vector, and wildlife such as bats account for a higher percentage of the cases.

Factors that may affect the outcome of exposure include the virus variant, dose of the virus, route and location of exposure, and host factors such as age and immune status. Without post-exposure prophylaxis, an estimated 20% of people bitten by rabid dogs develop rabies. Once the symptoms appear, the disease is almost always fatal within 3 weeks, even with intensive care. There have been only 6 reported cases of survival through the acute illness. Two people recovered well, without severe neurological sequelae. Both of these people had antibodies to the rabies virus at the time of the diagnosis, and diagnostic tests based on the detection of the virus were negative. Four survivors were left with severe neurological complications. Five survivors had been treated with a rabies vaccine before or soon after exposure, and before the symptoms developed. One young girl (who survived and recovered well) received no rabies prophylaxis because she had rabies virus-neutralizing antibodies at diagnosis. Some survivors might have had post-vaccinal encephalomyelitis rather than rabies.

Infections in Animals

Species Affected

All mammals are susceptible to rabies. There are many strains of the rabies virus; each strain is maintained in particular reservoir host(s). Important maintenance hosts include members of the Canidae (dogs, jackals, coyotes, wolves, foxes and raccoon dogs), Mustelidae (skunks, martens, weasels and stoats), Viverridae (mongooses and meerkats), and Procyonidae (raccoons), and the order Chiroptera (bats). Cat-adapted rabies variants have not been seen, although cats are often infected with rabies viruses from other hosts, and they can readily transmit the virus.

The important reservoir hosts vary with the area. In North America, maintenance hosts for rabies virus include insectivorous bats, striped skunks (*Mephitis mephitis*), raccoons (*Procyon lotor*) coyotes (*Canis latrans*) and various species of foxes. Red foxes (*Vulpes vulpes*), insectivorous bats, wolves and raccoon dogs (*Nyctereutes procyonoides*) appear to be important hosts in Europe. The canine rabies variant is well controlled in the U.S., Canada and Europe, and it may no longer be circulating or circulates only at low levels in some areas.

However, this virus has apparently become established in some wildlife populations, such as gray foxes (*Urocyon cinereoargenteus*) in Texas and Arizona, and it could be re-established in dogs from these reservoirs.

Canine rabies continues to be a significant problem in areas of Africa, Asia, the Middle East, and Latin America. Wildlife hosts may also be present. Both insectivorous and vampire bats are hosts for rabies virus in Mexico, Central and South America. Vampire bats (*Desmodus rotundus*) are sometimes responsible for outbreaks among cattle in South America. Rabies has also been reported in various other wildlife species, including wolves, coyotes, skunks and foxes, in Central and South America. Red foxes and golden jackals (*Canis aureus*) are often involved in wildlife rabies in the Middle East. Red and arctic foxes, raccoon dogs, mongooses and jackals are hosts for the virus in parts of Asia. Mongooses are also important in the Caribbean. In Africa, there is evidence that the virus may be maintained in jackals, foxes, mongooses, genets and other species.

Incubation Period

The incubation period varies with the amount of virus transmitted, virus strain, site of inoculation (bites closer to the head have a shorter incubation period), host immunity and nature of the wound. In dogs and cats, the incubation period is 10 days to 6 months; most cases become apparent between 2 weeks and 3 months. In cattle, an incubation period from 25 days to more than 5 months has been reported in vampire bat-transmitted rabies.

Clinical Signs

The initial clinical signs are often nonspecific and may include apprehension, restlessness, anorexia or an increased appetite, vomiting, a slight fever, dilation of the pupils, hyperreactivity to stimuli and excessive salivation. The first sign of post-vaccinal rabies is usually lameness in the vaccinated leg. Animals often have behavior and temperament changes, and may either become unusually aggressive or uncharacteristically affectionate. Pigs typically have a very violent excitation phase at the onset of disease. These signs usually last for 2 to 5 days, and may be followed by a phase in which either the paralytic or the furious form of rabies predominates.

The paralytic ("dumb") form of rabies is characterized by progressive paralysis. In this form, the throat and masseter muscles become paralyzed; the animal may be unable to swallow and it can salivate profusely. There may be facial paralysis or the lower jaw may drop. Ruminants may separate from the herd, become somnolent or depressed, and rumination may stop. Ataxia, incoordination and ascending spinal paresis or paralysis are also typical of this form. The paralytic form of rabies may be preceded by a brief excitatory phase, or none at all. Biting is uncommon. Death usually occurs within 2 to 6 days, as the result of respiratory failure.

The furious form is associated with infection of the limbic system, and is the predominant form in cats. It is characterized by restlessness, wandering, howling, polypnea, drooling and attacks on animals, people or inanimate objects. Animals with this form often swallow foreign objects such as sticks, stones, straw or feces. Wild animals often lose their fear of humans, and may attack humans or animal species they would normally fear (e.g., porcupines). Nocturnal animals may be seen in the daylight. Cattle may appear unusually alert. Convulsions can occur, particularly in the terminal stages. In the furious form of rabies, death sometimes occurs during a seizure but, in most cases, incoordination and ascending paralysis are seen late in the disease. The animal usually dies 4 to 8 days after the onset of the clinical signs.

The clinical signs are rarely definitive, and it may be difficult to distinguish the furious and dumb forms. The most reliable signs are behavioral changes and unexplained paralysis. In some cases in cats, no behavioral changes were noticed, and the illness appeared to begin as ataxia or posterior weakness, followed by ascending paralysis. Horses and mules are often distressed and extremely agitated, which may be interpreted as colic. Laryngeal paralysis can cause a change in vocalizations, including an abnormal bellow in cattle or a hoarse howling in dogs. Diagnosis can be difficult in rabbits and rodents unless there is a history of exposure to a potentially rabid animal, such as a raccoon. Some infected rabbits have had obvious neurological signs, often of the paralytic form, but others have developed only a nonspecific illness before death, or had other signs that were not initially suggestive of rabies. In one report, sudden death was the only sign in many infected squirrels. Some animals may die within a day, without marked clinical signs. Survival is extremely rare once the clinical signs appear.

Communicability

All species can transmit the virus to humans and other animals, but the efficiency of transmission varies with the host species and the form of rabies. Animals with the furious form of rabies are more likely to disseminate rabies than animals with the paralytic form. Carnivores are also more efficient vectors, in general, than herbivores. Herbivore-to-herbivore transmission is uncommon. Insectivorous bats have been implicated in most recent human cases in the U.S.

Virus shedding occurs in 50-90% of animals, depending on the host species and the infecting strain; the amount of virus found in the saliva varies from a trace to high titers. Shedding can begin before the onset of clinical signs. Cats excrete virus for 1 to 5 days before the signs appear, cattle for 1 to 2 days, skunks for up to 14 days and bats for 2 weeks. Virus shedding in dogs is usually said to

be limited to the 1 to 5 days before the onset of clinical signs; however, in some experimental studies (using viruses of Mexican or Ethiopian origin), the virus was present in the saliva for up to 13 days before the first clinical signs.

Asymptomatic carriers are thought to be very rare among domesticated animals. Possible cases have been reported among dogs in Ethiopia and India, including one experimentally infected dog that recovered from clinical rabies and carried the virus in her saliva and tonsils, but not the brain or other organs.

Post-Mortem Lesions

There are no characteristic gross lesions. The stomach may contain various abnormal objects, such as sticks and stones. The typical histological signs, found in the central nervous system, are multifocal, mild, polioencephalomyelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells, and glial nodules. Negri bodies can be seen in some but not all cases.

Diagnostic Tests

In animals, the rabies virus is usually identified by immunofluorescence in a brain sample taken at necropsy. The virus might also be found in other tissues such as the salivary gland, skin (tactile facial hair follicles) and corneal impression smears, but detection is less efficient. Immunofluorescence can identify 98-100% of cases caused by all genotypes of the rabies and rabies-related viruses, and is most effective on fresh samples. Other tests to detect the virus include immunohistochemistry and enzyme-linked immunosorbent assays (ELISAs). RT-PCR is also useful, particularly when the sample is small (e.g., saliva) or when large numbers of samples must be tested in an outbreak or epidemiological survey. Histology to detect aggregates of viral material in neurons (Negri bodies) is nonspecific, and it is not recommended if more specific techniques are available.

A single negative test does not rule out infection; therefore, virus isolation in cell culture (mouse neuroblastoma or baby hamster kidney cells) is often done concurrently. Mouse inoculation may also be used in some circumstances. Identification of variant strains is performed in specialized laboratories with monoclonal antibodies, specific nucleic acid probes, or RT-PCR followed by DNA sequencing.

Serology is occasionally used to test seroconversion in domesticated animals before international travel or in wildlife vaccination campaigns. It is rarely useful for the diagnosis of clinical cases, as the host usually dies before developing antibodies. Serological tests include virus neutralization tests and ELISAs. There is some cross-reactivity between the rabies virus and rabies-related viruses.

Treatment

There is no treatment once the clinical signs appear. Few studies have been published on post-exposure vaccination protocols for animals, and these procedures are often considered to be inadvisable because they may increase human exposure. In the U.S., post-exposure prophylaxis of animals has not been validated and is not recommended. Post-exposure prophylaxis of livestock and pets, using commercial vaccines licensed for this purpose, is practiced in some Asian countries including India.

Prevention

Rabies can be prevented in domesticated animals by vaccination and by the avoidance of contact with rabid wild animals. Rabies vaccines are available for dogs, cats, ferrets, cattle, sheep and horses. Both inactivated and modified live vaccines are effective, but rare cases of post-vaccinal rabies have been reported with the modified live vaccines in dogs and cats. Vaccines have not been validated in rabbits or rodents, although they might be used extralabel in petting zoos or other facilities where animals are in contact with many people. Wild animals can be immunized with oral vaccines distributed in bait. In countries with large stray dog populations, similar vaccines may be useful. Conventional rabies vaccines do not seem to protect animals against rabies-related viruses in phylogroup II (Mokola virus and Lagos bat virus); these viruses have caused fatal disease in vaccinated animals. Some cross-protection seems to exist with rabies-related viruses in phylogroup I.

Preventing animals from roaming will reduce the risk of exposure to rabid wild animals. To protect pet rabbits and rodents, they should be housed indoors, and watched closely if they are allowed outside to exercise. Rabbits kept outside should be kept in an elevated, double-walled hutch that does not have exposed wire mesh floors. As much as possible, domesticated animals should be kept from contact with wildlife, especially those that behave unusually. Bats caught by cats should be submitted for rabies testing.

To prevent the transmission of rabies to humans or other animals (as well as to prevent unnecessary prophylaxis in people who have been exposed), unvaccinated animals that have been exposed should be euthanized and tested. Alternatively, they may be placed in strict isolation for 6 months, with vaccination of dogs, cats and ferrets either upon entry into isolation or 1 month before release. Livestock, rabbits and other animals are isolated but not necessarily vaccinated. Vaccinated animals are revaccinated and confined under observation for at least 45 days. Animals with expired vaccinations are evaluated on a case-by-case basis. Asymptomatic dogs, cats or ferrets that have bitten humans (with no history of exposure to rabies) are currently observed for 10 days; if the animal develops

signs of rabies during this time, it is euthanized and tested for rabies. Countries free of the rabies virus may require a prolonged quarantine period before animals can be imported.

Morbidity and Mortality

Canine rabies remains common in Africa, Asia, the Middle East and Latin America. In the U.S., Canada and Europe, canine rabies has become uncommon or is absent, and most cases are seen in wildlife. In the U.S., 35% of all animal cases were reported in raccoons, 23% in skunks, 26% in bats and 7% in foxes in 2008. Domesticated animals account for less than 10% of all cases documented annually in the U.S.; most cases are seen in cats, cattle and dogs. Vaccination has decreased the number of rabies cases in dogs from 5,000 in 1946 to 75 in 2008. Currently, cats are more likely to develop rabies than dogs, due to the lower vaccination rates in this species. Although rabies often occurs as sporadic cases in domesticated animals, epizootics are sometimes reported among wildlife such as kudu (*Tragelaphus strepsiceros*) in Africa, or in cattle bitten by vampire bats in South America. Rabies can also be a serious problem among rare or endangered species. In Africa, the Ethiopian wolf (*Canis simensis*) and African wild dogs (*Lycaon pictus*) are threatened by this virus.

Factors that affect the outcome of exposure include the virus variant, dose of virus, route and location of exposure, and host factors such as age and immune status. The percentage of exposed animals that does not become ill is unknown. One experimental study reported that 8 of 47 dogs inoculated with rabies survived, and were subsequently resistant to reinfection. Another study reported the survival of 4 of 10 inoculated dogs; all four dogs developed antibodies to the virus. Symptomatic rabies is almost always fatal. A few, very rare, cases of recovery after street virus or vaccine virus-induced rabies have been reported in animals.

Internet Resources

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/rabies/m

Compendium of Animal Rabies Prevention and Control, 2008
http://www.cdc.gov/mmwr/pdf/rr/rr5702.pdf

International Veterinary Information Service (IVIS)
http://www.ivis.org

Medical Microbiology
http://www.gsbs.utmb.edu/microbook

Public Health Agency of Canada. Material Safety Data Sheets
http://www.phac-aspc.gc.ca/msds-ftss/index.html

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

World Health Organization
http://www.who.int/mediacentre/factsheets/fs099/en/

World Organization for Animal Health (OIE)
http://www.oie.int/

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/eng/normes/mmanual/a_summry.htm

OIE International Animal Health Code
http://www.oie.int/eng/normes/mcode/A_summry.htm

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*Link defunct as of 2009