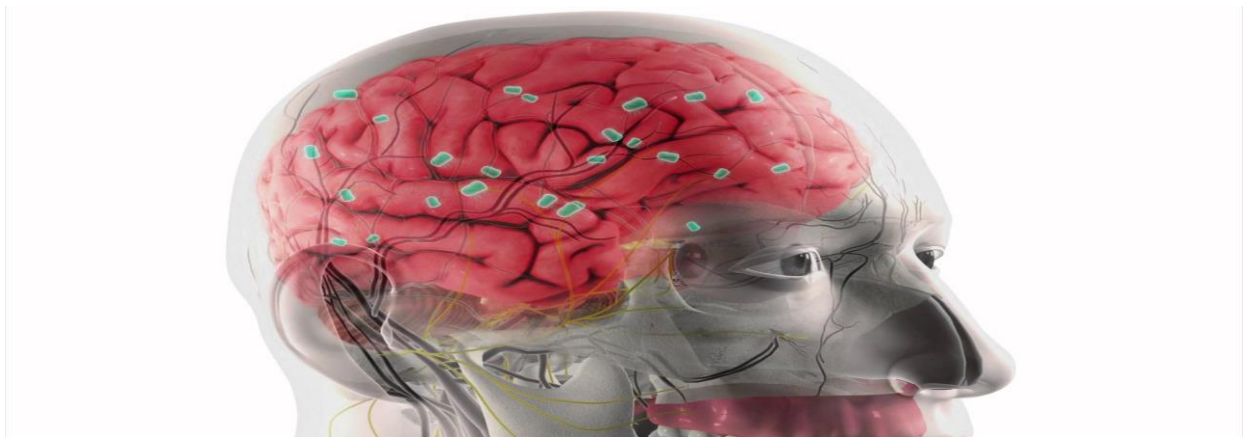




# Rabies virus



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## Historical

Rabies virus was recognized in Egypt before 2300 B.C. and was described by Aristotle in ancient Greece. Rabies virus. It has been characterized by many as one of the oldest and most feared diseases of both animals and man. It is the most lethal of all infectious diseases and has the widest host range of any virus. It was also responsible for inspiring one of the most significant biomedical discoveries in history. Rabies virus causes an inflammation of the brain, and is almost always fatal once symptoms develop.

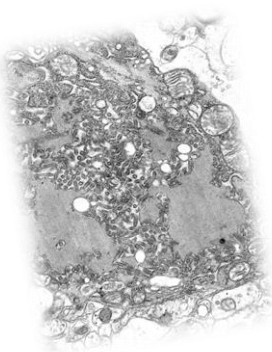
In wild and domestic animals, rabies virus may affect the part of the brain which regulates behavior, causing the animal to attack without fear or provocation. The rabies virus may also cause other changes in animal behavior, such as disorientation, impaired mobility, and unusual vocalizations. Wild animals that are normally out only at night may be seen during the day, approaching humans and domestic pets that they ordinarily would avoid. In the earlier part of this century, 1898 First Confirmed Case of Animal Rabies in Los Angeles , 1899 First Human Rabies Death in the City of Los Angeles . at 1958 Southern California Veterinary Medical Association Started Public Rabies Vaccination Clinics for Dogs Over 30,000 dogs were vaccinated that year at a cost of \$1.50/dog

New Jersey had a large problem with canine rabies. In 1939, the worst year for recorded cases of dog rabies, 675 dogs and four humans died of rabies. In 1942, a rabies program focused on the mass vaccination



of dogs and pick-up of stray animals was initiated. As a result of these efforts, New Jersey experienced its last case of the canine rabies strain in 1956. In 1885 Louis Pasteur developed the rabies vaccine during a time when the nature of viruses was still a mystery. It was the success of this vaccine that inspired scientists to prevent infectious diseases by vaccination.

### **The spread of disease:**



Rabies virus infection most commonly occurs when a rabid animal bites an individual. Rabies can also occur when infected saliva from a rabid animal contaminates an open wound (one which was bleeding within the past 24 hours), a scratch or skin abrasion, or a mucous membrane. In addition to saliva and the salivary glands, tissues and fluid of the central nervous system (i.e., brain and spinal cord) can contain high amounts of the virus. Virus is rarely found in other body organs and fluids. People cannot get rabies by just petting an animal, or even by getting saliva contaminated with rabies virus onto their intact skin. In order for them to get rabies, they must be bitten or the virus must come in contact with a recent wound or break in the skin or onto their mucous membranes (such as into the eye or mouth). However, any physical contact with a bat should be carefully evaluated for rabies preventative treatment. Bats have such tiny teeth that a bite may go undetected.

### **Epidemiological**

Rabies is a zoonosis which is prevalent in wildlife. that infects domestic and wild animals through close contacts with saliva from infected animals. The annual number of deaths worldwide caused by rabies is

estimated approximately 55,000 by World Health Organization (WHO). There has been no indigenous rabies case in Japan since 1957; however, there was only one imported case, a traveler who was bitten by a stray dog in Nepal and died in 1970.

Dogs in Asia and Africa remain the main reservoir and transmitter of rabies to humans. The others are mainly coyotes, foxes, jackals, mongooses, raccoons, skunks, wolves and bats. The efficacy of the current human and veterinary vaccines against emergent lyssaviruses should be evaluated because the newly discovered rabies-related viruses have been isolated from bats. The main animals involved differs from continent to continent.

<b>Europe</b>	fox, bats
<b>Middle East</b>	wolf, dog
<b>Asia</b>	dog
<b>Africa</b>	dog, mongoose, antelope
<b>N America</b>	foxes, skunks, raccoons, insectivorous bats
<b>S America</b>	dog, vampire bats



### Classification:

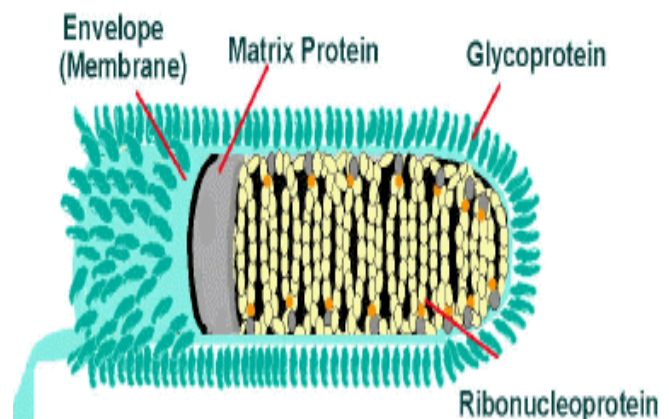
Rabies is caused by negative strand RNA-viruses belonging to the genus *Lyssavirus*, family *Rhabdoviridae* of the order *Mononegavirales*. The RNA genome of the virus encodes five genes whose order is highly conserved. These genes code for nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and the viral RNA polymerase (L).

The complete genome sequences range from 11,615 to 11,966 nt in length. The rabies virus has a bullet like shape with a length of about 180 nm.



## Virulence factors:

The virions have projections on the outer surface that protrude out 5-10 nm. These projections are made up of the glycoproteins the rabies virus encodes for five different proteins. First off, it encodes for nucleoprotein which tightly encases the genomic RNA.



It also codes for phosphoprotein which is associated with RNA. The matrix protein is associated with both the envelope and the RNA, and acts as the central protein for rhabdovirus assembly.

The glycoprotein codes for the 400 or more trimeric spikes that are arranged all over the viral surface. Finally, polymerase is associated with the RNA dependent RNA polymerase.

The G protein is involved with the fusion of the rabies virus envelope to the host. It ultimately helps with the attachment which further leads to the fusion. The polymerase encoded for by the virus transcribes mRNA from the single RNA strand. Once this strand of mRNA is translated, it results in the N, P, M, G, and L proteins

## Transmission

People usually get rabies from the bite of a rabid animal. It is also possible, but quite rare, that people may get rabies if infectious material from a rabid animal, such as saliva, gets directly into their eyes, nose, mouth, or a wound.

Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material (such as brain tissue) from a rabid animal constitute non-bite exposures.

Occasionally reports of non-bite exposure are such that post exposure prophylaxis is given.

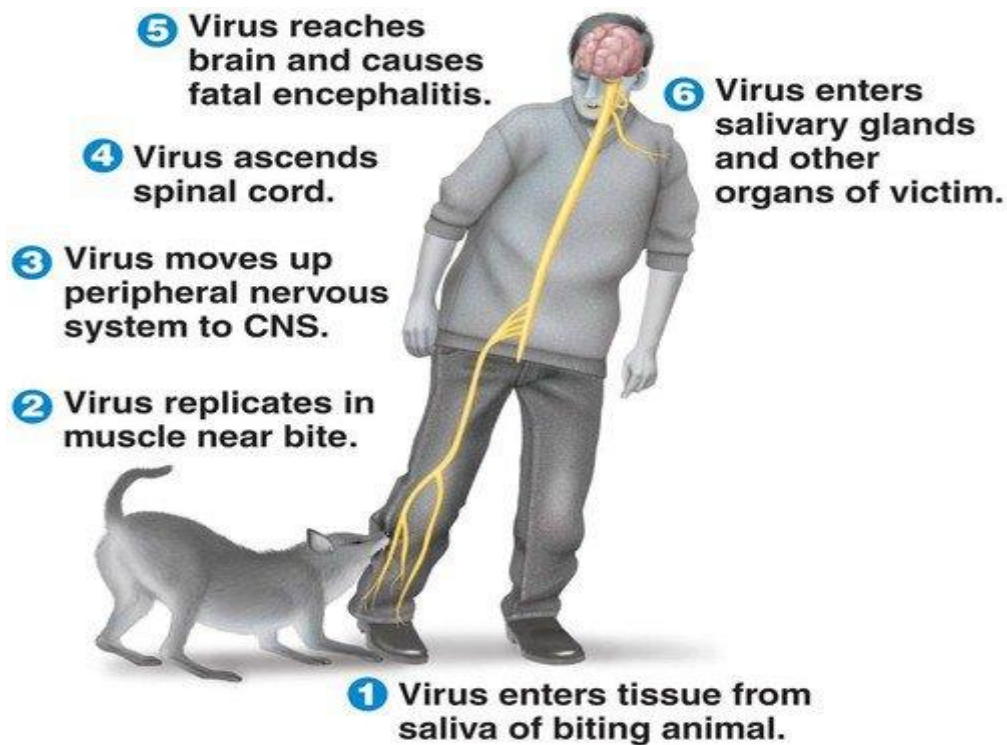
Inhalation of aerosolized rabies virus is also a potential non-bite route of exposure, but except for laboratory workers, most people won't encounter an aerosol of rabies virus.

Other contact, such as petting a rabid animal or contact with the blood, urine or feces of a rabid animal, does not constitute an exposure.

The only well-documented cases of rabies caused by human-to-human transmission occurred among eight recipients of transplanted corneas, and recently among three recipients of solid organs. Guidelines for acceptance of suitable cornea and organ donations, as well as the rarity of human rabies in the United States, reduce this risk.

In addition to transmission from cornea and organ transplants, bite and non-bite exposures inflicted by infected humans could theoretically transmit rabies, but no such cases have been documented. Casual contact, such as touching a person with rabies or contact with non-infectious fluid or tissue (urine, blood, feces) does not constitute an exposure and does not require post exposure prophylaxis. In addition, contact with someone who is receiving rabies vaccination does not constitute rabies exposure and does not require post exposure prophylaxis.

After a typical human infection by bite, the virus enters the peripheral nervous system. It then travels along the nerves towards the central nervous system. During this phase, the virus cannot be easily detected within the host, and vaccination may still confer cell-mediated immunity to prevent symptomatic rabies. Once the virus reaches the brain, it rapidly causes encephalitis and symptoms appear. This is called the "prodromal" phase and at this time, treatment is usually unsuccessful. Rabies may also inflame the spinal cord producing myelitis.



## Penetration

After the initial attachment. Virus enters the cell by either direct fusion with the plasma membrane or by adsorptive or receptor mediated endocytosis. Both processes have been described for rabies virus entry into cultured cells and neurons, although no information is available on entry into muscle in vivo. Iwasaki et al. and Perrin et al. observed fusion of virus partials with the cell membrane of BHK cells. Endocytosis of virus partials has been described in BHK cells and CER cells. In the latter, virus partials were observed in coated pits and vesicles. The lysosomotropic agent  $\text{NH}_4\text{Cl}$  and chloroquine, which act to raise the pH of endosomes and prevent fusion of virus with the endosome membrane, prevented rabies virus infection. These results suggest that, as the other enveloped viruses, the major mechanism of rabies virus entry into cells is endocytosis of the receptor-virus complex within coated pits and vesicles into acidic endosomes. Within the endocytic vesicle, acidic pH leads to



fusion of the virus membrane with the membrane of the vesicle. The viral genome is extruded into the cytoplasm and replication begins.

### **Replication cycle:**

The effectiveness of these genes and the rabies viral replication cycle have made it one of the most successful viral infections with an almost 0% survival rate once symptoms emerge. Following contact with an infected animal, the rabies virus must first be able to attach onto the cells of its new host. It does this through use of its viral spikes and membrane bound glycoprotein which interact with receptors already present on the host cell such as nicotinic acetylcholine receptors, low-affinity nerve growth factor receptors, neural cell-adhesion molecules, and gangliosides to allow for adsorption.

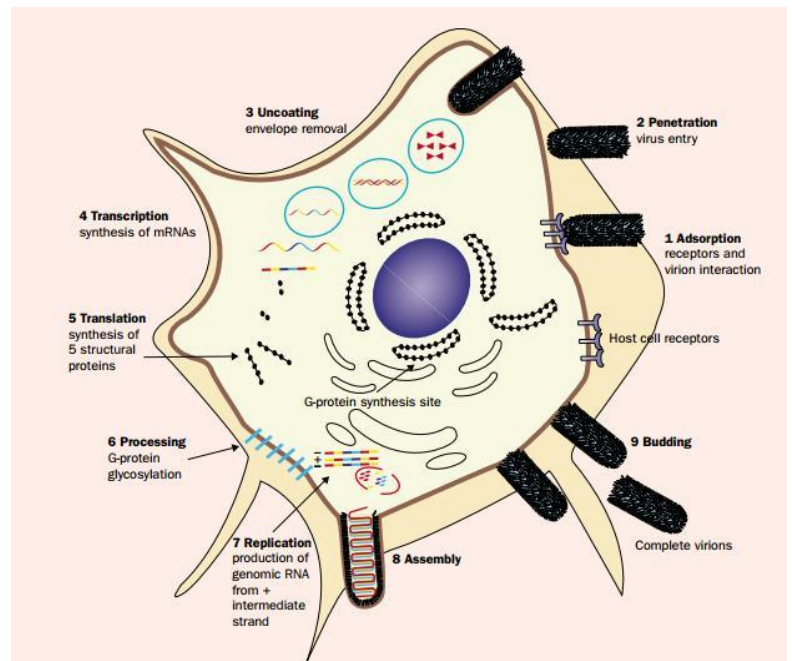
Once attached, the virus penetrates the cell through endocytosis where it is transported into an endosome and allowed to aggregate. It gains access into the cytoplasm of the host through fusion of its envelope with the membrane of the endosome, which releases its ribonucleocapsid. Given the negative-strand nature of the rabies RNA genome, the virus must first transcribe its viral genes using its L protein polymerase to create specific mRNAs corresponding to each of its five proteins. Once the genes have been transcribed to mRNA, the virus takes over the cell's metabolism using free ribosomes in the cell to translate the mRNA into their respective viral proteins. The G protein is unique in this process as it goes through further alteration in the cell endoplasmic reticulum and Golgi apparatus and is stored in the membrane of the host. Depending on the amount of N protein accumulated in the cell, the virus will shift between translation and replication.

To initiate replication, the virus must first begin making full length copies of the positive strand of its mRNA to serve as a template for

complete genome replication, which it achieves by ignoring the stop codons during synthesis.

## Assembly and budding

After sufficient replication has taken place, assembly occurs starting with formation of the ribonucleocapsid by a complex of proteins N, P and L. The ribonucleoprotein core is then covered to a capsule by the matrix protein and moves towards the host's membrane where it interacts with glycoproteins bound there to complete assembly of the virus. The virus gains an envelope and completes its replication cycle following budding from its host membrane, which releases the virus to infect other cells.



## The signs and symptoms of rabies

The first symptoms of rabies may be very similar to those of the flu including general weakness or discomfort, fever, or headache. These symptoms may last for days.

There may be also discomfort or a prickling or itching sensation at the site of bite, progressing within days to symptoms of cerebral dysfunction, anxiety, confusion, agitation. As the disease progresses, the person may experience delirium, abnormal behavior, hallucinations, and insomnia.

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

Disease prevention includes administration of both passive antibody, through an injection of human immune globulin and a round of injections with rabies vaccine.

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

### **Rabies diagnosed in animals:**

Rabies is diagnosed using the direct fluorescent antibody (DFA) test, which looks for the presence of rabies virus antigens in brain tissue. In humans, several tests are required.

Rapid and accurate laboratory diagnosis of rabies in humans and other animals is essential for timely administration of postexposure prophylaxis. Within a few hours, a diagnostic laboratory can determine whether or not an animal is rabid and inform the responsible medical personnel. The laboratory results may save a patient from unnecessary physical and psychological trauma, and financial burdens, if the animal is not rabid.

In addition, laboratory identification of positive rabies cases may aid in defining current epidemiologic patterns of disease and provide appropriate information for the development of rabies control programs.

The nature of rabies disease dictates that laboratory tests be standardized, rapid, sensitive, specific, economical, and reliable.

The DFA test is based on the observation that animals infected by rabies virus have rabies virus proteins (antigen) present in their tissues. Because rabies is present in nervous tissue (and not blood like many other viruses), the ideal tissue to test for rabies antigen is brain. The most important part of a DFA test is fluorescently-labeled anti-rabies antibody. When labeled antibody is incubated with rabies-suspect brain tissue, it will bind to rabies antigen. Unbound antibody can be washed away and areas where antigen is present can be visualized as fluorescent-apple-green areas using a fluorescence microscope. If rabies virus is absent there will be no staining.

### **Diagnosis in humans:**

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans; no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR).

Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

### **Rabies around the World**

Customarily, the level of international resources committed to the control of an infectious disease is a response to the associated human morbidity and mortality. For most infectious diseases, these data adequately reflect the deserved public health attention.

It is difficult, however, to estimate the global impact of rabies by using only human mortality data. Because vaccines to prevent human rabies have been available for more than 100 years, most deaths from

rabies occur in countries with inadequate public health resources and limited access to preventive treatment. These countries also have few diagnostic facilities and almost no rabies surveillance.

Underreporting is a characteristic of almost every infectious disease in developing countries, and increasing the estimated human mortality does not in itself increase the relative public health importance of rabies. There is, however, one often neglected aspect of rabies that does affect perception of its importance.

Rabies is not, in the natural sense, a disease of humans. Human infection is incidental to the reservoir of disease in wild and domestic animals; therefore, a more accurate projection of the impact of rabies on public health should include an estimate of the extent to which the animal population is affected and the expense involved in preventing transmission of rabies from animals to humans.

An additional figure is needed to complete the global picture of rabies. The best estimates of the impact of rabies on a country and the public health resources available within that country for rabies control are found in data for the number and distribution of cases of rabies in domestic animals. Despite evidence that control of dog rabies through programs of animal vaccination and elimination of stray dogs can reduce the incidence of human rabies, exposure to rabid dogs is still the cause of over 90% of human exposures to rabies and of over 99% of human deaths worldwide. The cost of these programs prohibits their full implementation in much of the developing world, and in even the most prosperous countries the cost of an effective dog rabies control program is a drain on public health resources. The estimated annual expenditure for rabies prevention in the United States is over US\$300 million, most of which is spent on dog vaccinations.

An annual turnover of approximately 25% in the dog population necessitates revaccination of millions of animals each year, and reintroduction of rabies through transport of infected animals from outside a controlled area is always a possibility should control programs lapse.

Reservoirs of wildlife rabies, virtually unknown in Asia and tropical regions, are also potential sources of rabies infection for dogs in Europe and North America.

### **Negri bodies:**

In 1903, most of the histopathologic signs of rabies were recognized, but rabies inclusions had not yet been detected. At this time, Dr. Adelchi Negri reported the identification of what he believed to be the etiologic agent of rabies, the Negri body. In his report, he described Negri bodies as round or oval inclusions within the cytoplasm of nerve cells of animals infected with rabies.

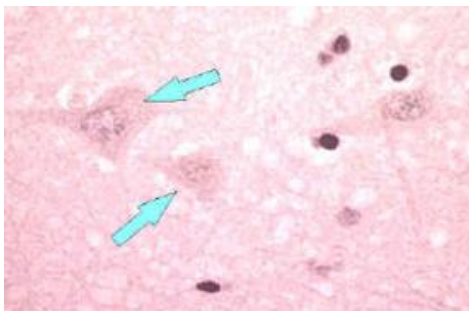
Negri bodies may vary in size from 0.25 to 27  $\mu\text{m}$ . They are found most frequently in the pyramidal cells of Ammon's horn, and the Purkinje cells of the cerebellum. They are also found in the cells of the medulla and various other ganglia.

Negri bodies can also be found in the neurons of the salivary glands, tongue, or other organs. Staining with Mann's, giemsa, or Sellers stains can permit differentiation of rabies inclusions from other intracellular inclusions. With these stains, Negri bodies appear magenta in color and have small (0.2  $\mu\text{m}$  to 0.5  $\mu\text{m}$ ), dark-blue interior basophilic granules.

The presence of Negri bodies is variable. Histologic staining for Negri bodies is neither as sensitive nor as specific as other tests. Some experimentally-infected cases of rabies display Negri bodies in brain tissue; others do not.



Histologic examination of tissues from clinically rabid animals show Negri bodies in about 50% of the samples; in contrast, the dFA test shows rabies antigen in nearly 100% of the samples. In other cases, non-rabid tissues have shown inclusions indistinguishable from Negri bodies. Because of these problems, the presence of Negri bodies should not be considered diagnostic for rabies.

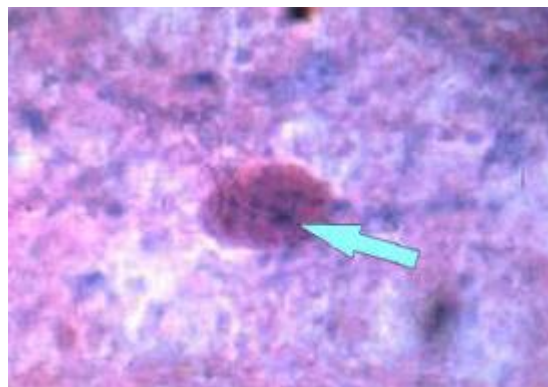


**What is the rabies?**

Once the rabies start, the universally fatal

**Controlling the**

**How can you animals?**



**prognosis of**

symptoms of disease is nearly

**disease:**

**prevent rabies in**

There are several things you can do to protect your pet from rabies.

First, visit your veterinarian with your pet on a regular basis and keep rabies vaccinations up-to-date for all cats, ferrets, and dogs.

Second, maintain control of your pets by keeping cats and ferrets indoors and keeping dogs under direct supervision.

Third, spay or neuter your pets to help reduce the number of unwanted pets that may not be properly cared for or vaccinated regularly.

Finally, call animal control to remove all stray animals from your neighborhood since these animals may be unvaccinated or ill.

### **The importance of vaccinating your pet**

Although the majority of rabies cases occur in wildlife, most humans are given rabies vaccine as a result of exposure to domestic animals. This explains the tremendous cost of rabies prevention in domestic animals in the United States.

While wildlife are more likely to be rabid than are domestic animals in the United States, the amount of human contact with domestic animals greatly exceeds the amount of contact with wildlife.

Your pets and other domestic animals can be infected when they are bitten by rabid wild animals. When "spillover" rabies occurs in domestic animals, the risk to humans is increased.

Pets are vaccinated by your veterinarian to prevent them from acquiring the disease from wildlife, and thereby transmitting it to humans.

### **How can you prevent rabies in people?**

Rabies in humans is 100% preventable through prompt appropriate medical care. Yet, more than 55,000 people, mostly in Africa and Asia, die from rabies every year - a rate of one person every ten minutes.

The most important global source of rabies in humans is from uncontrolled rabies in dogs. Children are often at greatest risk from rabies. They are more likely to be bitten by dogs, and are also more likely to be severely exposed through multiple bites in high-risk sites on the body.

Severe exposures make it more difficult to prevent rabies unless access to good medical care is immediately available.

This major source of rabies in humans can be eliminated through ensuring adequate animal vaccination and control, educating those at risk, and enhancing access of those bitten to appropriate medical care.

In 2006, a group of researchers and professionals formed a global Alliance for Rabies Control. They created and began inviting partners to join the World Rabies Day initiative.

The goal of this outreach is to mobilize awareness and resources in support of human rabies prevention and animal rabies control. The inaugural campaign on September 8, 2007 saw participation of nearly 400,000 individuals from at least 74 countries! This overwhelming response was an important step forward for rabies prevention and control and further illustrates the widespread recognition of the need for action to control this easily preventable disease.

What can you do?

- Vaccinate your pet
- Maintain control of your pets to reduce their exposure to wildlife
- Spay or neuter to decrease the number of stray animals
- Report any stray or ill animals to animal control

### **Treatment:**

Treatment is recommended if a health-care professional thinks that someone was exposed to a potentially rabid animal.

If the animal is a pet or farm animal that has no symptoms, the animal can be isolated and observed for 10 days. Wild animals that can be captured

can be killed and tested for the virus. If the animal can't be found, it is best to consult with the local health department.

The general pathway to determine post exposure prophylaxis (protective treatment) for rabies requires the following information:

Bite: Did a bite occur, and where is the location of the bite? (Any penetration of the skin is considered a bite; although bites to the face and hands carry the highest risk, all bites need to be considered for prophylaxis.)

Non-bite incident: Did the saliva touch an open wound or a mucous membrane?

Animal risk factors: No cases of rabies infection have been reported in the U.S. from fully vaccinated domestic dogs or cats.

Bats: Any contact with a bat that leads to a potential scratch, bite, or mucous membrane exposure to saliva needs to be evaluated. If prolonged exposure to a bat is discovered (sleeping in a room where a bat is found), postexposure prophylaxis needs to be considered.

As rabies is a fatal disease, it is often best to start the series of shots until further information is available.

A series of injections is given. The first is a rabies immune globulin that helps to prevent the virus from infecting the individual.

## **Vaccination:**

### **Rabies Vaccine**

A regimen of four 1-mL doses of HDCV or PCEC vaccines should be administered intramuscularly to previously unvaccinated persons.

The first dose of the four-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.

For adults, the vaccination should always be administered intramuscularly in the deltoid area (arm). For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for rabies vaccine injections because observations suggest administration in this area results in lower neutralizing antibody titers.

## Post exposure Prophylaxis for Non-immunized Individuals

Treatment	Regimen
<b>Wound cleansing</b>	All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
<b>RIG</b>	If possible, the <b>full dose</b> should be infiltrated around any wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.
<b>Vaccine</b>	HDCV or PCECV 1.0 mL, IM (deltoid area ), one each on days 0 , 3, 7, and 14.

*\* A 5th dose on day 28 may be recommended for immunocompromised persons.*

## Post exposure Prophylaxis for Previously Immunized Individuals

Treatment	Regimen
<b>Wound cleansing</b>	All post exposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.
<b>RIG</b>	RIG should <b>not</b> be administered.
<b>Vaccine</b>	HDCV or PCECV 1.0 mL, IM (deltoid area), one each on days 0 and 3.

If exposed to rabies, previously vaccinated persons should receive two IM doses (1.0 mL each) of vaccine, one immediately and one three days later. Previously vaccinated persons are those who have received one of the recommended pre exposure or post exposure regimens of HDCV, RVA, or PCECV, 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 pre-booster antibody titer.

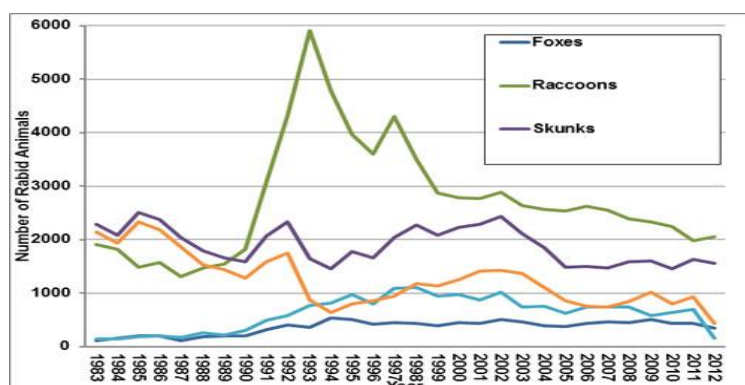
## Statistics and Recently discover:

Each year, scientists from the Centers for Disease Control and Prevention (CDC) collect information about cases of animal and human rabies from the state health departments and publish the information in a summary report. The most recent report, entitled "Rabies surveillance in the United States during 2013 [PDF -756KB][\[PDF\]](#)," contains the epidemiologic information on rabies during 2013. Below is a brief summary of the surveillance information for 2013, including maps showing the distribution of rabies in the United States.

In 2013, 49 states and Puerto Rico claimed 5,865 cases of rabies in animals and 3 human rabies cases to CDC. The total number of reported cases decreased by approximately 5% from those reported in 2012 (6,162 rabid animals).

## Wild Animals

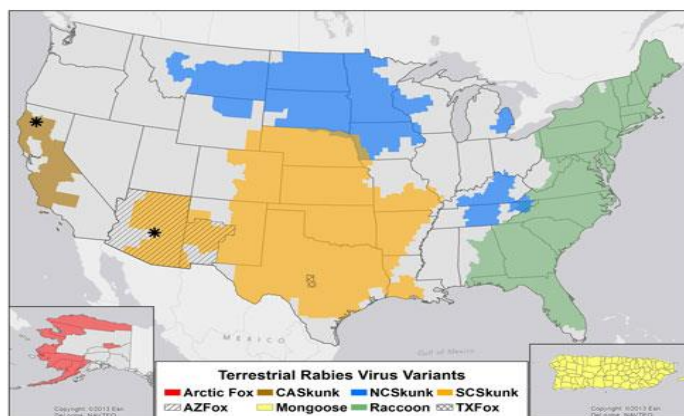
Wild animals accounted for 92% of reported cases of rabies in 2013. Raccoons continued to be the most frequently reported rabid wildlife species (32.3% of all animal cases during 2013), followed by bats (27.2%), skunks (24.6%), and foxes (5.9%).





Cases of rabies among wildlife in the United States, by year and species, 1984 to 2013.

Although raccoons were the most commonly reported rabid wildlife species during 2013, the 1,898 reported rabid raccoons represented a 2.82% decrease, compared with the 1,953 rabid raccoons reported during 2012. See distribution of major rabies virus variants in the United States and Puerto Rico on map below.



Distribution of major rabies virus variants among mesocarnivores in the United States and Puerto Rico, 2009 through 2013.

## Human Rabies

Human rabies cases in the United States are rare, with only 1 to 3 cases reported annually. Thirty-four cases of human rabies have been diagnosed in the United States since 2003, in which 10 cases were found to have contracted infection outside of the United States and its territories. The number of human deaths in the United States attributed to rabies has been steadily declining since the 1970's due to animal control and vaccination programs, modern rabies biologics following exposure, and successful outreach campaigns. Rabies vaccination programs have eliminated domestic dogs as reservoirs of rabies in the United States, although we still see 80 – 100 dogs and >300 cats with rabies each year, usually infected by wildlife when these domesticated pets are not

vaccinated against rabies. While the biggest rabies threat in the world (domestic dogs) has been controlled in the United States, interactions with other rabies reservoir species results in 30,000 – 60,000 Americans being vaccinated against rabies each year.

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