

# Rabies

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# Rabies

## Summary

- Rabies is caused by several closely related Rhabdoviruses
- Infection of the central nervous system: meningo-encephalitis
- Zoonosis
- Transmission via saliva of infected animals, very rarely aerogenic transmission
- Often long incubation time, usually 20-90 days, leaving a window for curative vaccination
- Muscle spasms, salivation, intermittent delirium, fever, hydrophobia
- If symptoms, 100% fatal
- Prevented by wound cleaning, antiserum and vaccination

## General

The genus of Lyssaviruses (Gr. "lyssa" = madness) includes rabies virus and a few other related viruses (Mokola, Duvenhage, Lagos bat virus, European bat lyssavirus 1 and 2, Australian bat lyssavirus, Irkut virus, Aravan virus, West Caucasian Bat virus, Bokelo bat lyssavirus, Ikoma Lyssavirus, rabies virus, Shimoni bat virus). Mokola virus was originally found in Nigeria in various shrews (*Crocidura*). Duvenhage virus was isolated from insectivorous bats in South Africa and Zimbabwe. They are all rhabdoviruses (Gr. "rhabdos" = rod, hence "rod-shaped viruses"), a term which is derived from their cylindrical, bullet shape under electron microscopy. Various subtypes can be distinguished with monoclonal antibodies and so the source of an infection can sometimes be traced.

Rabies is a viral infection that affects the central nervous system. It is a zoonosis affecting many mammals (dog, cat, fox, squirrel, ferret, skunk, raccoon, sheep, cattle, bat, etc.). Those which are mainly responsible for transmission to humans are dogs (Africa, Asia) and vampire bats (Central and South America). The latter feed mainly on cattle blood. Rabies infection produces a form of paralysis in cattle, sometimes leading to large losses of livestock. The virus is distributed world-wide except in New Zealand, West Malaysia and a number of islands such as Borneo, New-Guinea, Bali, Hawaii and Great Britain (although there was an endemic case in the UK in the early 21<sup>st</sup> century). Australia was rabies-free until 1995, when a rabies virus was discovered in flying foxes in that country. The number of cases of rabies is estimated as >50,000 per year. Four million people annually receive post-exposure prophylaxis.

## Transmission

Transmission occurs via the saliva of an infected animal as a result of a bite or of licking damaged skin or mucous membrane. Infected dogs, raccoons, cats, etc., can be responsible for transmission. In dogs, the saliva becomes infectious at least 2 days before symptoms of the disease appear. In extremely rare cases, asymptomatic dogs can excrete the virus for years. In principle, infection can also occur via aerosol, but this is rare (limited to bat-infested caves, laboratories). Transmission by eating contaminated meat has been described in animals but is not (yet) known in humans. To date, a few cases of human-to-human transmission have been described, 1 ascertained bite transmission. Transmission via corneal transplantation and organ transplantation has occurred. Successful transmission experiments were conducted as early as the beginning of the 19th-century, when saliva from a person with rabies was introduced into a healthy dog. Rabbits primarily exhibit paralytic rabies, which was of importance in the search for a vaccine (these animals were easier to study than convulsing rabid dogs).

### The type of exposure according to WHO

Category 1 exposure: touching, stroking or feeding a suspect or sick animal or being licked on intact skin

Category 2 exposure: nibbling of unprotected skin, minor scratches without bleeding, being licked on damaged skin

Category 3 exposure: transdermal bites or scratches, exposure of mucous membrane to saliva; exposure to bat bites or scratches

### Vampires

Bats are classified in their own order within the mammals. The Chiroptera (Gr. “cheiro” hand; “pteron” wing) includes approximately 900 species. An animal requires  $\pm$  20 ml of blood each day (half its body weight). In the wild, a vampire lives on average 10 years. Like its mythical human counterpart, the animal hunts at night. It lands in the vicinity of its victim (usually a cow) and then carefully creeps up close. The bat licks the hair of the pelt of the cow and then cuts away a small area with its teeth. It makes a 5 mm shallow wound with its razor-sharp, self-sharpening incisors (only in Hollywood do vampires bite with their canines). The animal licks up the blood that is discharged. The saliva contains anticoagulants (including a plasminogen activator that is being

studied as a new thrombolytic). Rabies virus may be found in the saliva. *Desmodus rotundus* can also sometimes drink blood from humans and then usually bites the nose, ears or lips. While feeding, the bat urinates on its prey. This probably helps it to find the animal again the following night. Vampires must have blood very regularly. They die if they cannot eat for two or three days. Vampires, are social animals and often regurgitate and share blood meal with their young and with fellow members of the same colony that have been unable to find any prey. As a result of this social behaviour, rabies virus spreads to other animals within the colony. Rabid bats can attack other animals without provocation, including other bats and humans. Bats can be asymptomatic carriers or become ill, exhibit aberrant behaviour and die from the infection. Bats can also spread histoplasmosis through their faeces.

In addition to their known role as biologic vectors of rabies to humans and domestic animals and surra (*Trypanosoma evansi*) to horses and cattle, vampire bats can also be temporary biologic as well as mechanical vectors of Venezuelan equine encephalitis virus and foot-and-mouth disease. They are likely to be effective mechanical vectors if not biologic vectors of any bloodborne pathogen, including HIV. Besides rabies virus, other viruses ascribed to bats have proven pathogenic or fatal to people and domestic animals. Four species of Australian *Pteropus* bats in Queensland carry Hendra virus without developing symptoms. These bats disseminate virus in urine or amniotic fluid during birthing, and the virus is later ingested by pregnant horses that amplify the virus, which then spreads to people and causes a fatal pneumonia (13/20 horses were infected in a 1994 outbreak, which resulted in two human deaths).

Nipah virus, identified in urine and saliva of *Pteropus* bats in Malaysia, spreads the virus to pigs and destroyed that country's swine industry in 1998. The virus spread from pigs to hundreds of industry workers; approximately 40% of these workers died of severe viral encephalitis caused by the agent. The symptoms are similar to Japanese encephalitis.

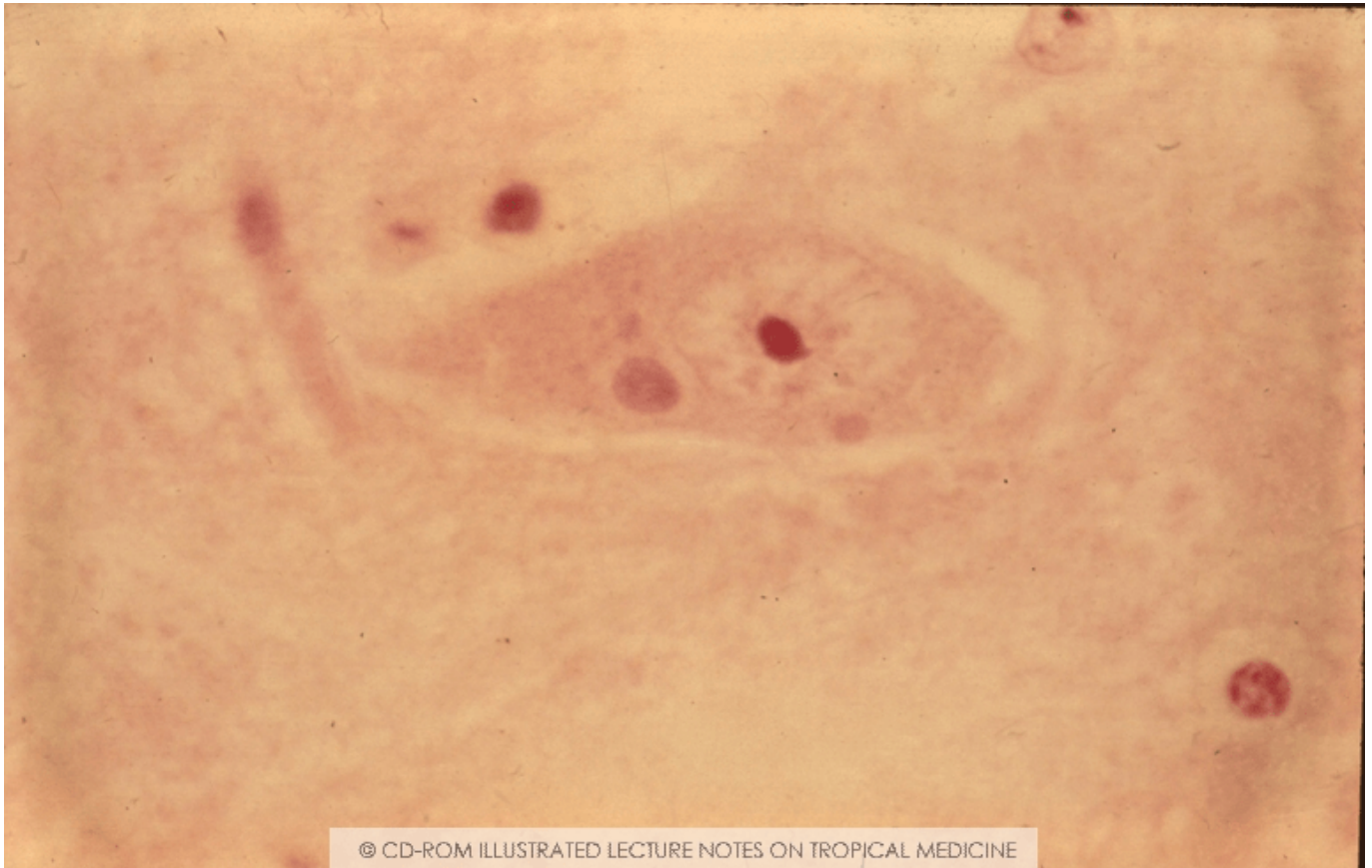
## Pseudorabies

In veterinary medicine, rabies should not be confused with pseudorabies or Aujeszky's disease. This viral condition (Suid herpes virus) predominantly attacks pigs (the only natural host), but can occasionally affect cattle, sheep, goats, dogs, cats and wild animals. Infections can be latent or clinically manifest, including involvement of the central nervous system with symptoms that include abnormal gait, intense scratching, self-mutilation, convulsions and death.

## Pathogenesis

After the virus has entered the body, it multiplies locally in myocytes and afterwards crosses the neuromuscular junction to penetrate a peripheral nerve. The virus enters nerve cells through nerve spindles of sensory nerves or neuromuscular junctions of motor nerves. Subsequently it spreads along the nerve by retro-axonal flow to the spinal cord and brain. In the central nervous system, the virus proliferates further. The nucleocapsid of the virus can be detected by microscopy in some neurons as spherical inclusions in the cytoplasm: Negri bodies [Adelchi Negri 1876-1912, assistant to Camillo Golgi in 1900]. From there, the virus again spreads to almost all organs in the body. The saliva contains high concentrations of infectious virus.

The patient develops a very aggressive viral encephalitis. This is supposed to be 100% lethal, although there may be some exceptions. Very occasional cases of rabies survivors –with and without treatment according to the Milwaukee protocol- have been published, be it with severe sequelae. In 2012, it was reported that in a remote part of the Peruvian Amazon where rabies secondary to vampire bats is common, unvaccinated people had antirabies antibodies in their blood. It is still unclear what this finding means exactly. It is not known if these people developed minor symptoms and recovered, asymptotically seroconverted after a very small inoculum with or without the help of bat oral flora, specific genetics in an isolated community, natural immunity, cross-reactivity with other germs or still something else.



Rabies. Some neurons contain intraneuronal inclusions which consist of viral nucleocapsid. These inclusions are known as Negri bodies.

## Clinical aspects

### General

Incubation lasts 20 to 90 days (extremes of 4 days and 6 years have been described). Bites close to the face and with a large inoculum (severe wounds) are associated with the shortest incubation times. A prodromal phase lasting 2 to 10 days then follows. The first symptom is an influenza-like syndrome with moderate fever and malaise lasting a few days. This can be associated with severe local pruritus leading to scratching and excoriations, headache, pain or paraesthesia at the site of the bite. Sometimes there is moderate muscle weakness. Local myxedema after muscle percussion can occur. Agitation and insomnia can occur at a very early stage. Afterwards the disease can take two different courses, depending on which features predominate: furious rabies on the one hand (more involvement of the brain) and paralytic rabies (extensive involvement of the spinal cord) on the other.

## Furious rabies

This form is more common accounting for about two thirds of the cases. There is increasing anxiety, excitation, hyperactivity, hyperventilation, disorientation and/or hallucinations. Symptoms occur intermittently and persist for 1 to 5 min, followed by a period of mental calm. Hyperstimulation occurs as a result of destruction of inhibitory centers in the brain stem. In approximately half the patients, painful spasms of the larynx and throat muscles occur (swallowing and vocal cord spasms). These are triggered for instance by seeing or wanting to drink a glass of water. This is associated with painful convulsive contractions of the respiratory muscles. The patient is therefore afraid of this situation (hydrophobia or fear of water). The spasms can also be induced by blowing air over the face (aerophobia) or by other, often minor, stimuli (compare with tetanus). The spasms develop into generalized convulsions. There is no trismus or muscle rigidity between convulsions (in contrast to tetanus). Neck stiffness can occur but is usually not pronounced. There is profound dysautonomia. The patient may sweat and weep profusely, as well as displaying hypersalivation, hypothermia, hypertension and tachycardia (involvement of the autonomic nervous system). Fever can occur. There is a pronounced thirst. The patient is in agony. Hypothalamic involvement can result in diabetes insipidus (insufficient ADH) or hypersecretion of antidiuretic hormone (SIADH). Myocarditis can cause cardiac arrhythmias. Coma follows within 10 days after the onset of the acute neurological symptoms and can persist for hours to months (mostly short-lasting). Finally, cardiac and respiratory arrest follow. Death occurs in nearly 100% of cases, in general 2-7 days after the onset of the disease. Medical management can prolong survival up to 133 days.

In the whole of the medical literature (up to 2016), about 15 people have been described who survived clinical rabies. Of these survivors, several received immune prophylaxis. In 2004, a 15-year-old girl who was bitten by a bat in Wisconsin survived rabies after treatment with coma induction, ketamine, midazolam, ribavirin, and amantadine. Later on, several patients have recovered with this regimen, but many failures of this new regimen have also been seen.

An immune response is essential for recovery from rabies, although vaccine would not need to be given if at the time of diagnosis- a patient had developed already rabies virus-specific antibody (controversial).





Rabies. Once symptoms have started, death is certain. The number of people who survived rabies is extremely low. Photo copyright Cochabamba, Bolivia

### **Differential diagnosis of furious rabies:**

**Delirium tremens:** chronic alcohol misuse and sudden abstinence, signs of hepatic injury (spider naevi, flapping tremor, gynaecomastia, collateral circulation, etc).

**Reaction to some hard drugs** (crack, speed). This occurs more often in some large cities.

**Strychnine poisoning.** This plant product suppresses nerve impulse inhibition and thus causes convulsions. All types of sensory stimuli can cause convulsions. Consciousness is clear if no asphyxia has occurred. It is sometimes used as a rodent poison. If the patient survives the first 24-hours, the prognosis is good. In the event of death, the rapid onset of rigor mortis is characteristic.

**Acute psychosis and hysteria.** Very common in developing countries. Hysteria: no hydrophobia if the patient is unaware of the existence of this sign.

**Tetanus:** portal of entry, trismus, muscle stiffness, convulsions on sudden stimulus, clear consciousness, mostly shorter incubation, no encephalitis, clear CSF.

**Bacterial meningitis:** lumbar puncture. Note that several organisms can cause lymphocytic pleiocytosis (*Brucella*, *Listeria*, *Treponema pallidum* (syphilis), *Borrelia*, tuberculosis, *Coxiella burnetii*, various rickettsiae, etc.). Various systemic fungal infections, sarcoidosis, auto-immune diseases (S.L.E.) with cerebral vasculitis etc. can produce abnormal cerebrospinal fluid.

**Cerebral abscess.** As a result of septic emboli (subacute bacterial endocarditis) or from penetration of a collection of pus (sinus, middle ear, etc.). Cerebral toxoplasmosis is common in AIDS.

**Viral encephalitis** due to herpes simplex or an arbovirosis such as Japanese encephalitis, West Nile fever, tick-borne encephalitis or Venezuelan equine encephalitis. Often no virus can be found. There are no lucid periods and no typical spasms. For arboviral infections, serology is important. Infections with Herpes virus B (*Herpes simiae* virus) are rare. This virus can be transmitted via a bite, scratch or via body fluids from an infected monkey. Mucocutaneous lesions and encephalitis can follow inoculation. (Val-)acyclovir or ganciclovir can be tried in treatment, but the infection provokes dramatic neurological symptoms.

**Cerebral malaria** (*Plasmodium falciparum*)

**Post rabies-vaccination encephalitis** if vaccination has been given with the old nerve tissue based vaccines.

**Bite of a cobra or other elapid** snake: saliva will dribble out of the mouth as a result of throat paralysis (not from spasms). Ptosis, swelling, pain and tissue injury at the site of the bite.

## Paralytic rabies

This is the most frequent form after a vampire bite (South America). There is a flaccid paralysis (no tendon reflexes). There are often mild sensory disorders. The paralysis often begins in the bitten part of the body and then ascends further. Death follows from general paralysis. The course is less rapid than in the furious form.

### **Differential diagnosis paralytic rabies:**

**Polio:** initially fever and muscle pain, asymmetrical paralysis, clear consciousness.

**Guillain-Barre syndrome:** ascending symmetrical paralysis, typical cerebrospinal fluid with large amount of protein but few cells. Early in this syndrome, the CSF might still be normal. Control lumbar puncture some days (up to a week) later then shows the albuminocytological dissociation. There are variants in which the cranial nerves are primarily affected (Fischer syndrome). It should be noted that initially the cerebrospinal fluid can be normal, but very quickly the protein level in the CSF will raise substantially. Often the syndrome follows one or more weeks after *Campylobacter* enteritis or another infection.

**Botulism:** descending paralysis (ocular muscles, throat muscles, neck, other muscles, progressive respiratory paralysis), no fever, dry mucous membranes, large pupils. Is caused by toxins produced by a specific bacterium (*Clostridium botulinum*), related to the organism that causes tetanus. The organism can be found in a wound or more often in spoiled food.

**Diphtheria:** is rare but poses few diagnostic problems in general in case of throat, nose or laryngeal infection. Extensive membrane-like coating in the throat ("diphthera" = leather) with marked cervical lymph node enlargement. This is followed 1 to 2 weeks later by carditis and progressive paralysis, sometimes also with sensory disorders (peripheral neuropathy). Cutaneous diphtheria produces painful wounds but rarely paralysis.

**Bite of an elapid snake** (e.g. cobra): rapidly occurring descending paralysis + local reaction at the site of the bite.

### **Metabolic / hypoxic / toxic encephalopathy**

**Reye syndrome:** sudden onset, often after an initial viral syndrome. Vomiting is frequent. There is hepatomegaly in 40% of cases and liver function tests are abnormal. A liver biopsy is diagnostic.

### **Differential diagnosis of dysphagia:**

Determine whether there is fever, whether pain occurs on swallowing and whether the dysphagia is high (throat area) or low (retrosternal). Include visual mouth examination.

**Foreign body in the throat or oesophagus:** sudden onset, history of swallowing fishbone, chicken

bone or hard piece of food, feeling that “something is stuck in the throat”, no fever if no complications. Beware of perforation of the oesophagus by sharp objects such as toothpicks. Mediastinitis can follow.

**Neurotoxic snake bite:** progressively worse, ptosis, cough and speaking becomes difficult, history of snake bite, often pain and swelling at the site of the bite. No fever if no complications.

**Infection of the mouth or throat** (viral, *Candida*, streptococci, abscess, aphthous stomatitis, etc.): painful, acute, visibly red throat/tonsils/abscess, fever, lymphadenopathy.

**Diphtheria** (is reported separately because of its important nature): inflamed throat with grey membranes (sometimes skin wound), lymphadenopathy, neuritis, sometimes with regurgitation of drink or food through nose, visual problems, paralysis and/or carditis, often no history of immunization.

**Rabies:** history of animal bite, signs of encephalitis with episodic hyperactivity and paralysis, sometimes hydrophobia. Fluctuating consciousness.

**Tetanus:** begins over the course of several days, often recent wound, no immunization, the mouth cannot be opened wide, muscle spasms over the rest of the body. Temperature fluctuating. Normal consciousness.

**Neurological disorders with paralysis of the palate** (e.g. bulbar poliomyelitis, bulbar tumour).

**HIV with candidiasis of the oesophagus:** check other clinical indicators, positive HIV test.

Oesophageal disorders such as **Chagas disease, stenosis, achalasia, tumours.**

## Diagnosis

The diagnosis is clinical. Rabies must be suspected in someone who develops neurological symptoms a week or more after an animal bite. The number of white blood cells in the peripheral blood is normal or slightly raised, with a slight elevation of monocytes. Albuminuria can occur. An EEG shows abnormalities consistent with encephalitis. A CT scan or NMR scan of the brain can show surprisingly few abnormalities. Hydrophobia occurs in approximately half the patients and is pathognomonic (i.e.: highly specific). Investigation of contact with animals is important, but no history of exposure can be found in 20% of patients. The protein content in the cerebrospinal fluid is usually normal and in the

first week of the disease the white blood cell count in the CSF is raised in 70% of cases (highly fluctuating differential count). Antibodies in serum and cerebrospinal fluid cannot be detected before there are symptoms. Antibodies against rabies virus cannot be detected in most laboratories in the tropics. The virus may be detected in corneal smears. The test is highly specific, but there are many false negatives and in most cases the technique is not available (fluorescein-conjugated antirabies serum). The virus is sometimes detectable by immunofluorescence in a skin biopsy, which is best taken from the neck (many hair follicles surrounded by nerve endings). Isolation of the virus from saliva, urine and cerebrospinal fluid (not from blood) is possible, but in tropical practice not feasible. The best technique is reverse transcriptase PCR on saliva (detection of rabies RNA). After death, the diagnosis can be established retrospectively by a brain biopsy. Negri bodies (intraneuronal inclusions consisting of viral nucleocapsid) are detectable in 80% of patients. All in all, rabies is a clinical diagnosis, but this has to be supported with arguments, such as:

1. RT-PCR on saliva for rabies RNA
2. Virus isolation from saliva or cerebrospinal fluid
3. Corneal smear for rabies virus antigen
4. Antibodies in serum
5. Skin biopsy for immunofluorescence

## Rabies in the animal

The incubation period in dogs is 2 weeks to 6 months. Rabies in dogs (and also in cats and horses) leads to changes in behaviour, aggressiveness, running away from home, difficulty in swallowing with hypersalivation, and convulsions. The animal can exhibit a more paralytic presentation with dysphagia and a drooping lower jaw (more so in the fox and cattle). Sometimes the hind legs give way. The animal usually dies within 7-10 days. Rabies in animals is not universally fatal. In case of a bite from a dog suspected of rabies, the dog should be observed for ten days. If it exhibits abnormal behaviour, the animal's brain can be analyzed. Negri bodies will only be present if the animal has shown clear signs of rabies. If the animal is killed immediately, the opportunity of making or excluding a diagnosis via this method is lost. If state-of-the-art technical facilities are available, however, it is better to kill the animal immediately and to detect rabies virus in the spinal cord or brain. This will rarely be possible in tropical regions. If the animal cannot be found (e.g. after a scratch by a bat), treatment of the human victim should follow on the assumption that it was infected.



Cow dying of rabies. Copyright ITM

## Treatment

Since there is quasi 100% mortality once symptoms have occurred, only palliative therapy can be given at that time: pain relief (morphine) and reduction of spasms (myorelaxants e.g. diazepam). In most cases, barbiturates and chlorpromazine are also given. Although no case of transmission from patient to medical personnel has yet been described, it is recommended that the patient should be isolated and staff should wear masks, goggles and gloves during the provision of care. Staff should also preferably be vaccinated, but that is not obligatory.

In 2004, Jeanna Giese became the first patient ever to recover from rabies without the vaccine. She survived with a treatment based on a chemical-induced coma and intense anti-excitotoxic strategy combined with antivirals. The treatment -called the "Milwaukee protocol"- comprised ketamine-induced coma, together with high doses of benzodiazepines (midazolam) and supplemental barbiturates, ribavirin and amantadine. Normally, ribavirin penetrates little into the cerebrospinal fluid, but in rabies the permeability of the blood-brain barrier is higher. Ribavirin might also protect against rabies myocarditis. Amantadine (200 mg/day) has in vitro activity against rabies virus, and

has intrinsic anti-excitotoxic properties. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist with specific activity against rabies in animal models. It is possible that the NMDA-receptor may be one of the rabies virus receptors. Ketamine inhibited the genome transcription of rabies virus and restricted viral spread in an experimental rat model. Benzodiazepines and barbiturates are gamma-aminobutyric acid (GABA)-receptor agonists.

Unfortunately, attempts to replicate the successful (modified) Milwaukee protocol have been discouraging. In 2019, about 14 adequately documented survivors of rabies have been reported worldwide, five of them from India. Most survivors had received at least 3 anti-rabies vaccines initiated on the day of the bite. Almost all survivors have moderate to severe neurological sequelae with poor functional outcomes. The focus on treatment and management of rabies should not draw away attention from the core objective, which is unarguably the “prevention” of human rabies.

### **What to do after a potentially infected bite?**

**Clean the wound with a detergent (soap).** It is extremely important to wash the wound immediately with soap and water for 15 minutes, because the virus is very sensitive to cleaning agents. Afterwards the wound should be disinfected with iodine/isobetadine or 60-80% ethanol. Oxygenated water or mercurochrome are not indicated. Leave the wound open afterwards (no primary closure of bite wounds).

**Tetanus vaccination** status should be checked and tetanus vaccination +/- immunoglobulins should be given if needed.

**Antibiotics:** All bites are by definition bacterially contaminated but do not always become infected. Wound infection with *Pasteurella multocida* or *Capnocytophaga canimorsus* is frequent after dog or cat bites. Routine administration of antibiotics after bite wound is not recommended. Antibiotics should be given if there are clinical signs of surinfection (dolor, tumor, calor, rubor) or in severely contaminated wounds.

### **Evaluation of the contact of the animal with the skin**

The measures to be taken following a contact with a possible rabid animal depend on the type of contact, the immune status of the patient, the endemicity of the region and the type animal.

#### WHO EXPOSURE RISK CATEGORIES

Category I	<ul style="list-style-type: none"> <li>• Tactile contact (stroking) or feeding the animal</li> <li>• Licking of the intact skin</li> </ul> <p><i>In other words: no exposure</i></p>
Category II	<ul style="list-style-type: none"> <li>• Gnawing the uncovered and originally intact skin</li> <li>• Superficial lesions from scratches or grazes, without bleeding.</li> <li>• Licking of non-intact skin</li> </ul>
Category III	<ul style="list-style-type: none"> <li>• Single or multiple bites or scratches that penetrate the dermis</li> <li>• Contact with the mucous membranes via the saliva after licking</li> <li>• Licking a grazed or broken skin</li> <li>• (Possible) scratches and bites of bats: often no visible lesion or the feeling of a bite</li> </ul>



ANIMALS	CATEGORY I	CATEGORY II	CATEGORY III	IMMUNE SUPPRESSION CATEGORIES II and III	Rabies- PrEP in good order
<b>WILD LAND MAMMALS SUCH AS FOX, WOLF, RACON ...</b>					
<b>Endemic</b>	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
<b>Non-endemic: Suspected</b>	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
<b>Non-endemic: Not suspected</b>	None	None	None	None	None
<b>MONKEY (WILD)</b>					
<b>Endemic</b>	None	SCHEDULE 2	SCHEDULE 2	SCHEDULE 3	SCHEDULE 1
<b>DOG, CAT, FERRET</b>					
<b>Endemic</b>	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
<b>Non-endemic: (Imported fewer than 12 months previously)</b>	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
<b>Non-endemic: Suspected</b>	None	SCHEDULE 2	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1
<b>Non-endemic: Not suspected</b>	None	None	None	None	None
<b>BAT</b>					
<b>Endemic and non-endemic:</b>	<b>None* or Schedule 3</b>	SCHEDULE 3	SCHEDULE 3	SCHEDULE 3	SCHEDULE 1

- Schedule 1: vaccination Day 0 and Day 3 or intradermal vaccination (4x 0.1 ml) on Day 0
- Schedule 2: vaccination Day 0 (2x), Day 7, Day 21
- Schedule 3: RIG Day 0 + vaccination Day 0, 3, 7, 14 and 28
- Rabies PrEP in good order: rabies pre-exposition prophylaxis before the bite (Day 0 and 7)

**Human anti-rabies immunoglobulins** (RIG (Rabies Immune Globulin) – e.g. Berirab®, Imogam Rabies-HT®) are administered as soon as possible after the bite, whereby the largest possible amount is administered via a deep local injection in and around the bite with the aim of locally neutralizing the virus. The amount of MARIG depends on the anatomical location or locations of the injury and the

size of the lesions, with a maximum dose based on body weight (20 IU/kg). MARIG administration at an anatomical site different from the site of the bite is no longer recommended. Following mucosal contact with saliva of a potentially rabid animal without injury (category III), MARIG is no longer indicated.

**Vaccination** in humans was first carried out by Louis Pasteur in 1885. Vaccination is possible in view of the long incubation time. Antibodies are present after 7-14 days. There are several vaccines and therapeutic post-exposure vaccination regimens. WHO currently strongly recommends the safer modern cell-culture or embryonated-egg vaccines (CCEEV's). CCEEVs contain inactivated rabies virus that has been grown in embryonated duck or chicken eggs or in cell culture (e.g. primary chick embryo cells, Vero cells or human diploid cells). The viral harvest is concentrated, purified, inactivated and lyophilized. In some CCEEVs, human albumin or processed gelatine is used as a stabilizer.

If rabies immunoglobulins are not available, schedule 2 is always the preferred schedule (2 injections on day 0, 1 injection day 7 and 21). If it is not possible to complete the full schedule with the same brand of vaccine, another brand may be used. The WHO has documented the interchangeability of Verorab®, Rabipur®, HDCV Rabiës®.

Because preventive vaccination (pre-exposure prophylaxis) does not provide complete protection, PEP booster vaccinations are still necessary for vaccinated individuals following a type II or III contact: rabies PEP schedule 1.

## Prevention

Do not touch any sick, paralyzed animals, or better still: simply never touch animals in the wild.

Kill stray dogs (sometimes problematical in Buddhist countries).

Vaccinate dogs (pets).

Vaccination of wild animals: for example in Switzerland and Germany foxes are vaccinated with oral live vaccine incorporated in fishmeal pellets or other bait. Vampire bats can be vaccinated by catching some and applying the live vaccine to the skin. The animals often lick one another and it would be possible in this way to vaccinate a colony of animals. The vaccine could also be applied to cattle.

Persons in high-risk occupations (e.g. veterinarians, certain laboratory personnel, medical personnel

in the infectious diseases departments of hospitals), and certain travellers to high endemic regions) should receive PrEP vaccination. It could also be considered in populations living in rabies endemic areas, where the dog bite incidence is high. WHO currently recommends a 2-day intradermal regimen at Day 0 and Day 7.

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