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Canine and feline rabies

Dr Djemai Samir

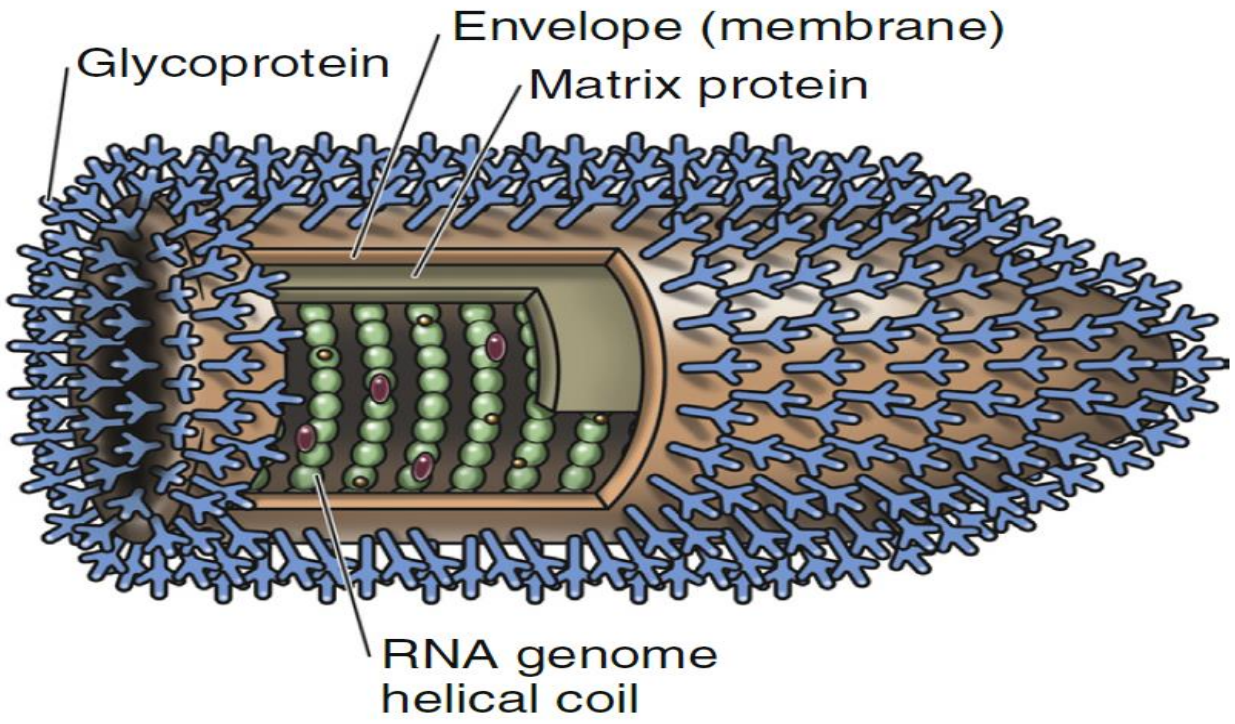
- Rabies is a viral anthropozoonosis that is always fatal once clinical signs appear.
- Acute and progressive encephalomyelitis caused by neurotropic viruses of the Rhabdoviridae family belonging to the Lyssavirus genus, which can affect most mammals (warm-blooded animals = homeotherms), including humans.
- The disease develops when the virus enters the body through a wound (most often a bite) or through mucous membranes.

- The disease affects a wide range of carnivores - primary hosts of lyssaviruses - including dogs, foxes, raccoons, skunks, mongooses, and various species of bats.
- Accidentally transmissible to humans.
- Rabies is present worldwide and is estimated to cause approximately 60,000 human deaths each year.
- Disease legally recognized as contagious and must be reported.

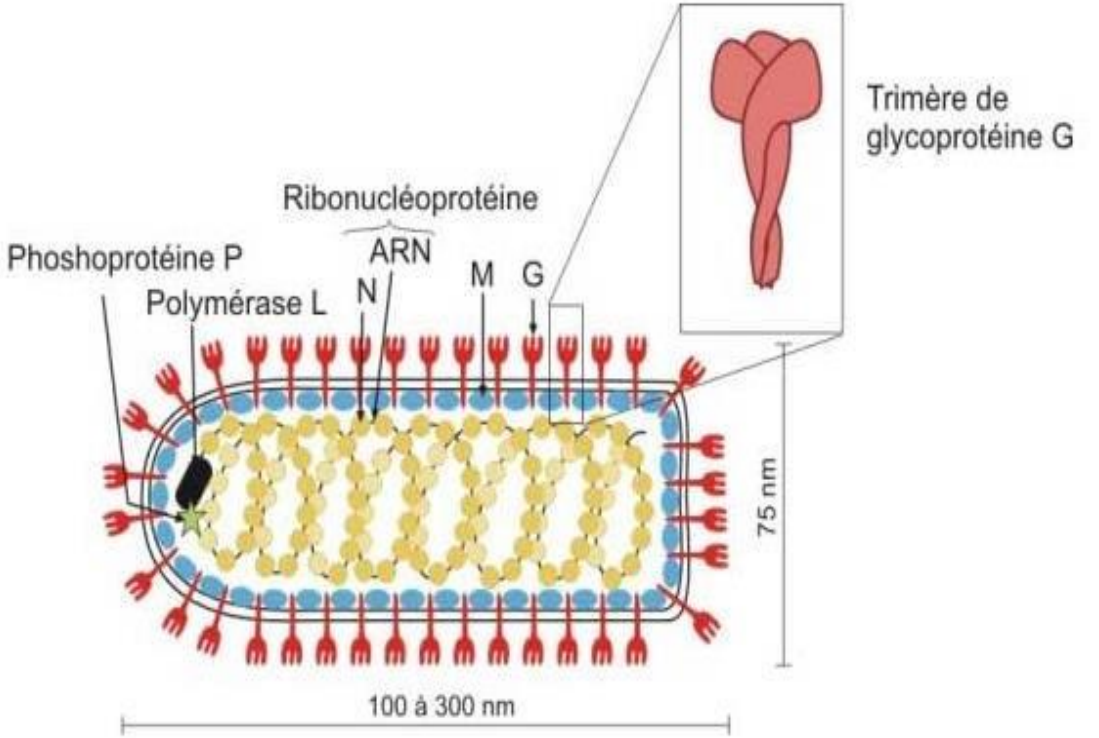
Etiological agent and epidemiology

- Rabies is caused by an enveloped, neurotropic RNA virus, bullet-shaped, belonging to the Rhabdoviridae family, genus Lyssavirus (Lyssa, Greek goddess of madness, rage, and fury).

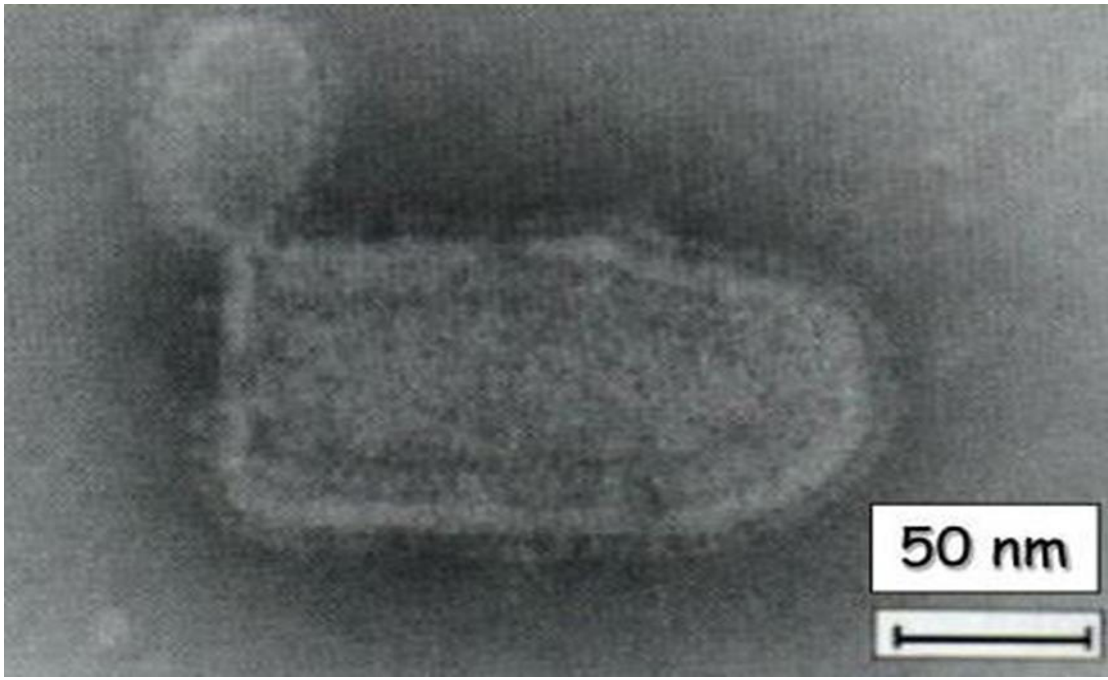
Structure of a rabies virus virion.



The glycoprotein binds to cellular receptors present on many types of tissues: muscle, nervous, skin, glandular tissues (salivary glands, etc.)



Rabies virus (Electron microscope)

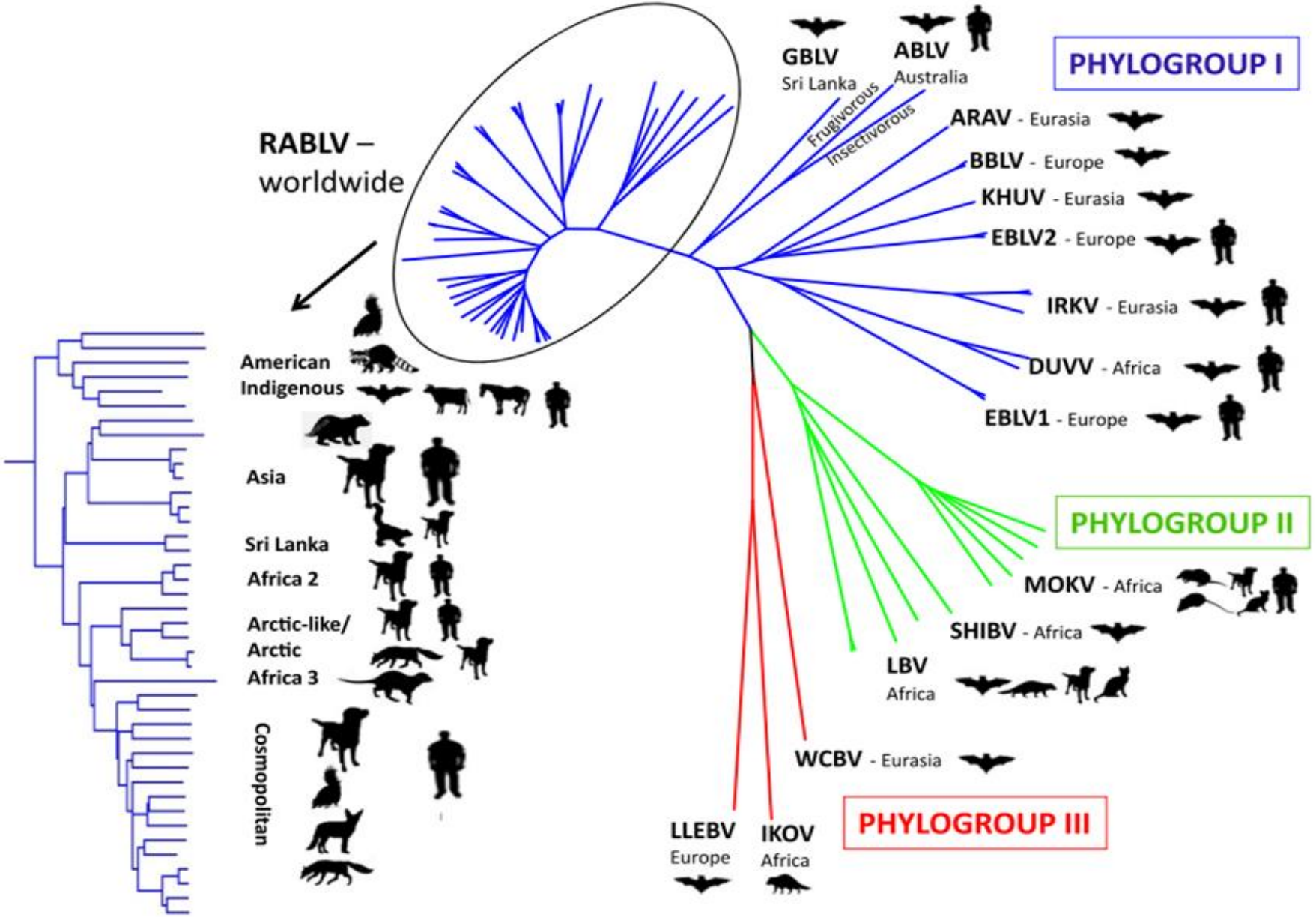


- This virus is fragile in the environment and is easily inactivated by various disinfectants, soaps, ultraviolet rays, and heat.
- It can survive for up to 3 or 4 days in carcasses at 20 °C, and longer in the refrigerator.
- Freezing tissues at temperatures below −20 °C can prolong the survival of the virus for years.

- The development of genetic characterization techniques for viruses (genomic sequencing) has led to the observation of many lyssaviruses, which have been classified into 17 distinct viral species (or 17 genotypes) = 1-17 genotypes.
- The sequence of the viral genome coding for the N protein (nucleoprotein) determines the different genotypes.

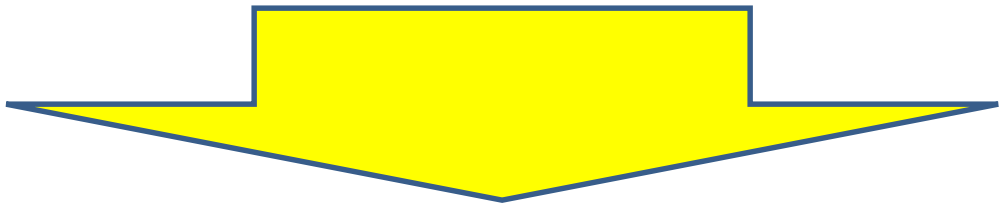
- The genotypes are divided into three phylogroups (Vega et al., 2021):

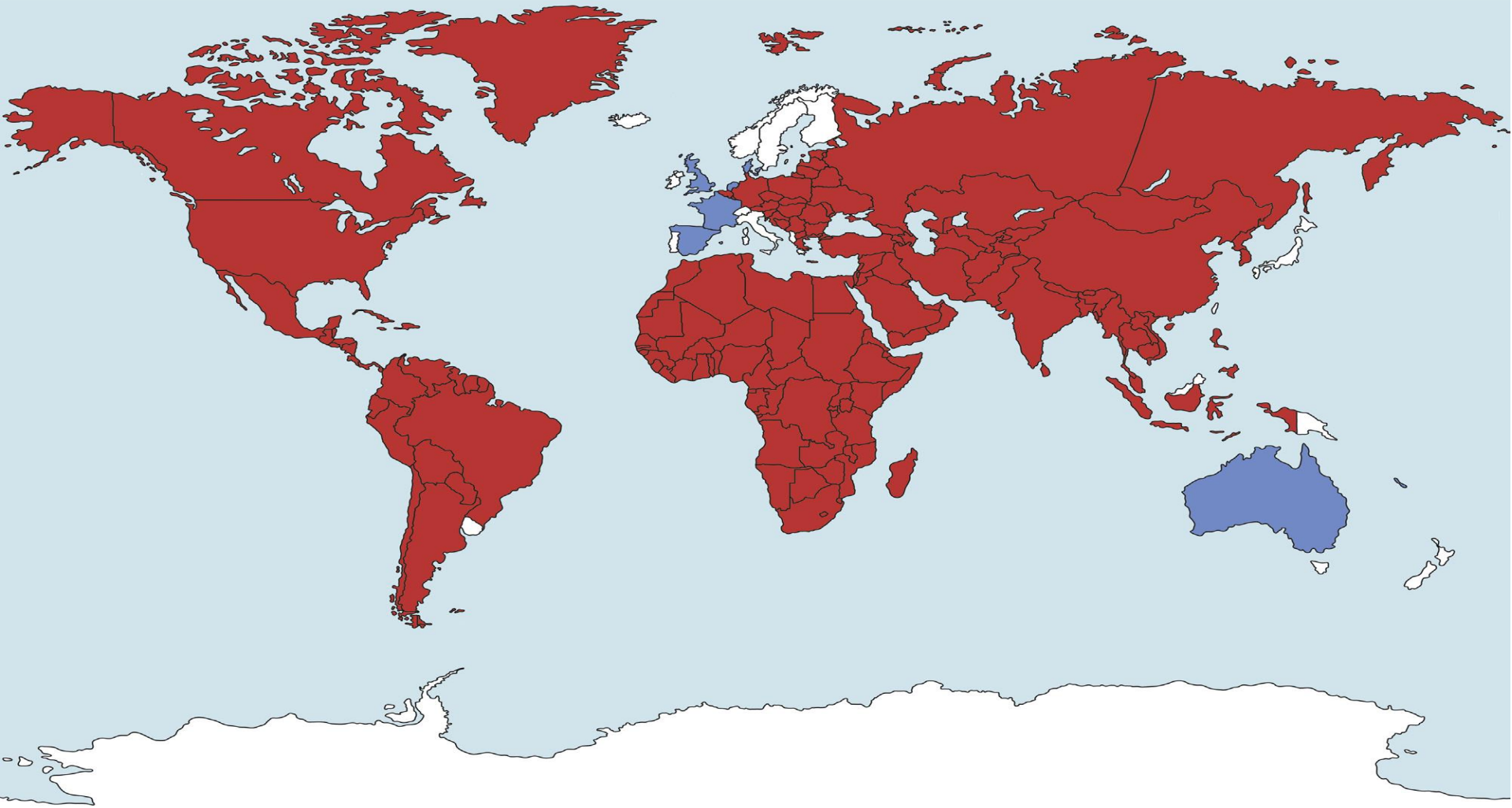
- **Phylogroup I: Rabies lyssavirus (RABV or genotype 1), Duvenhage lyssavirus (DUVV), Bokeloh bat lyssavirus (BBLV), European bat−1 lyssavirus (EBLV-1), European bat−2 lyssavirus (EBLV-2), Gannoruwa bat lyssavirus (GBLV), Australian bat lyssavirus (ABLV), Aravan lyssavirus (ARAV), Khujand lyssavirus (KHUV), Irkut lyssavirus (IRKV), Kotalahti bat lyssavirus (KBLV).**
- **Phylogroup II: Lagos bat lyssavirus (LBV), Mokola lyssavirus (MOKV), Shimoni lyssavirus (SHIBV).**
- **Phylogroup III-IV: West Caucasian bat lyssavirus (WCBV), Ikoma lyssavirus (IKOV), Lleida bat lyssavirus (LLEBV).**



Phylogenetic analysis of globally circulating lyssaviruses

- Although Taiwan, Australia, New Zealand, Iceland, the United Kingdom, Japan, most of Western Europe, Fiji, Hawaii, and Guam are considered rabies-free (classical).
- Lyssaviruses capable of causing fatal encephalitis in humans exist in some of these regions, notably in Australia, Western Europe, and the United Kingdom.





Global distribution of lyssaviruses. Distribution of rabies virus (red). Areas where only rabies-related viruses, and not the classical genotype 1, are reported and classified by WHO as 'rabies-free' (dark blue). White areas are free of rabies and related viruses.

- There are 7 major lyssavirus genotypes = 1 to 7:

- **The classical rabies virus belongs to genotype 1.**
- The other 6 genotypes primarily infect bats and cause a rare, fatal human encephalitis, clinically indistinguishable from classic rabies.

The 7 most well-known genotypes:

Génotype	Virus	Distribution géographique	espèces concernées	Efficacité du vaccin
1	**Rage classique**	**mondiale**	**Homme**, carnivores sauvages et domestiques, chauves-souris.	oui
2	Lagos bat	Afrique	chauves-souris frugivores, chats, chiens.	**non**
3	Mokola	Afrique	**Homme**, musaraignes, chats, chiens, rongeurs.	**non**
4	Duvenhage	Afrique du Sud	**Homme**, chauves-souris insectivores.	**non**
5	EBL-1	Europe	**Homme**, chauves-souris insectivores.	**partielle**
6	EBL-2	Europe	**Homme**, chauves-souris insectivores.	oui
7	ABL	Australie	**Homme**, chauves-souris frugivores et insectivores.	oui

– **EBL** = European Bat Lyssavirus (**bat** = chauve-souris) – **ABL** = Australian BL

Transmission

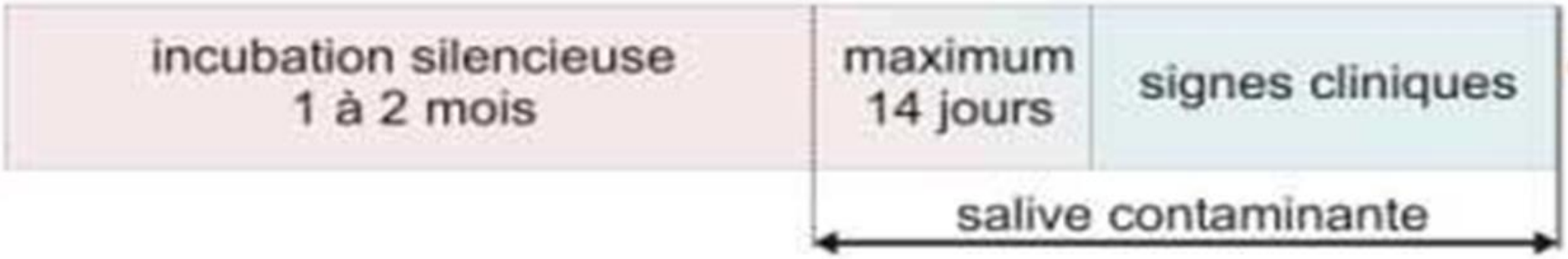
- Infection with the rabies virus most often occurs through inoculation into a wound via saliva containing the virus = usually after a bite (especially from a dog); scratches or licking of open wounds.
- The rabies virus can be transmitted through mucous membranes (conjunctiva, nasal mucosa, etc.) if they come into contact with infectious materials such as the saliva of an infected animal.

Other routes of transmission, rare in species other than dogs and cats, include:

- Cornea or solid organ transplantation in humans*.
- Aerosol transmission (aerosolized virus), as in caves harboring numerous bats.
- Transmission after ingestion of infected biological tissues or milk.

* Maier T, Schwarting A, Mauer D, et al. Management and outcomes after multiple corneal and solid organ transplantations from a donor infected with rabies virus. Clin Infect Dis. 2010;50:1112-1119.

- Infected animals are contagious 1 to 7 days (or even longer) before the appearance of clinical signs → death.
- Handling dead animals is dangerous = the virus retains its virulence in the corpse for a more or less prolonged period.



Sensitive species and reservoirs

- All warm-blooded animals are susceptible to rabies = Mammals.
- Mammals are the only known vectors in nature.

1. Natural reservoir hosts of the virus: Dogs, wild carnivores (foxes, coyotes, jackals, wolves, raccoons, civet dogs, skunks, mongooses, badgers, etc.) and bats (a wide range of bat species).

Skunks

Grey foxes

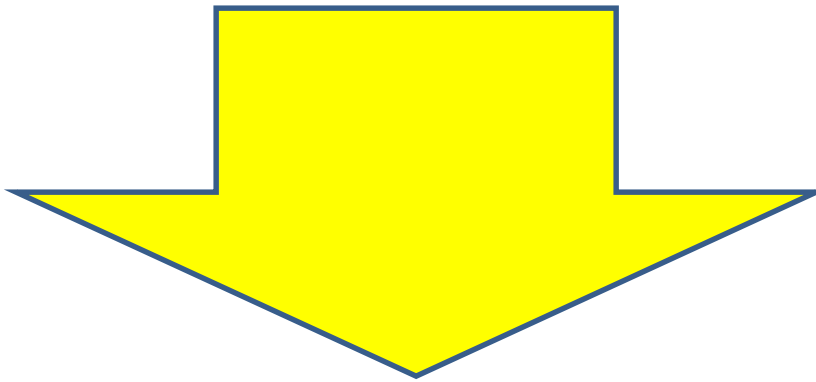
Grey foxes (grey foxes)

African golden wolf
(Loup doré africain)

Mongoose
(Mangouste)

2. Accidental hosts:

- In general, wolves, foxes, coyotes, jackals, dogs, cattle, raccoons, skunks, bats, and mongooses are highly sensitive to infection.
- Cats, ferrets, primates, sheep, goats, and horses are moderately sensitive.



- Cats are actually more resistant than dogs to experimental infection by certain strains of the canine rabies virus.
- Young animals are generally more sensitive to rabies than older ones.
- Marsupials, particularly opossums, are less sensitive.

Female opossum (Didelphis virginiana) carrying young.

- Birds have low susceptibility:
  - Natural infection of birds by the rabies virus is rarely documented.
  - The occurrence of rabies in chickens in the wild is considered extremely rare.
  - A case of naturally acquired rabies infection in a chicken (Gallus domesticus) has been reported in India*.

* Baby, J., Mani, R. S., Abraham, S. S., Thankappan, A. T., Pillai, P. M., Anand, A. M., Madhusudana, S. N., Ramachandran, J., & Sreekumar, S. (2015). Natural Rabies Infection in a Domestic Fowl (Gallus domesticus): A Report from India. PLoS Neglected Tropical Diseases, 9(7), e0003942. https://doi.org/10.1371/journal.pntd.0003942

- In all host species, rabies is generally an acute and fatal disease, although some animals, like bats and skunks, show a more prolonged course of the disease than others, such as foxes, coyotes, or raccoons.
- The possibility of an asymptomatic carrier state, particularly in bats and in certain reservoir host species, has been suggested based on the detection of anti-rabies antibodies and the virus.

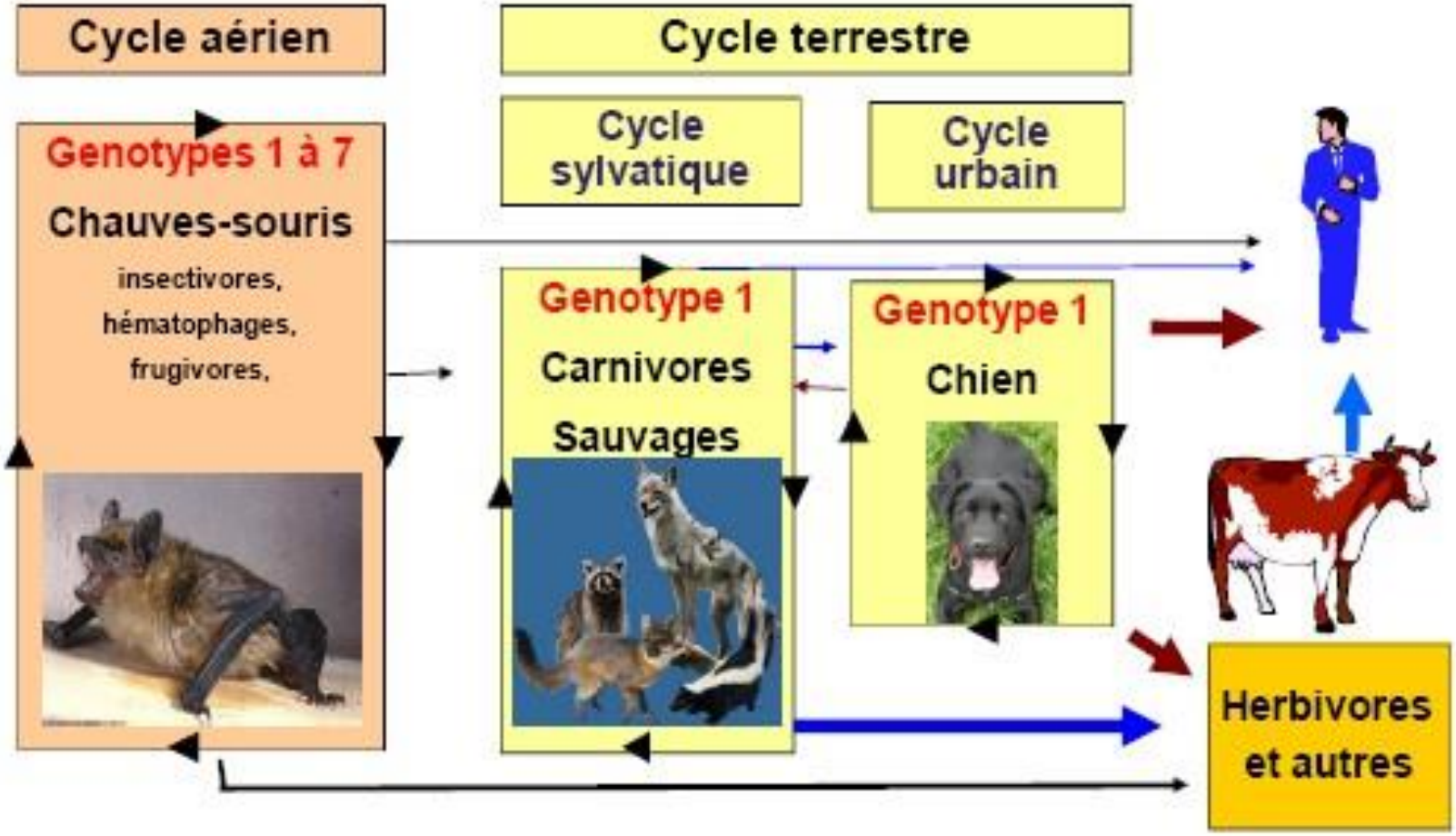
Rabies epidemiological cycle

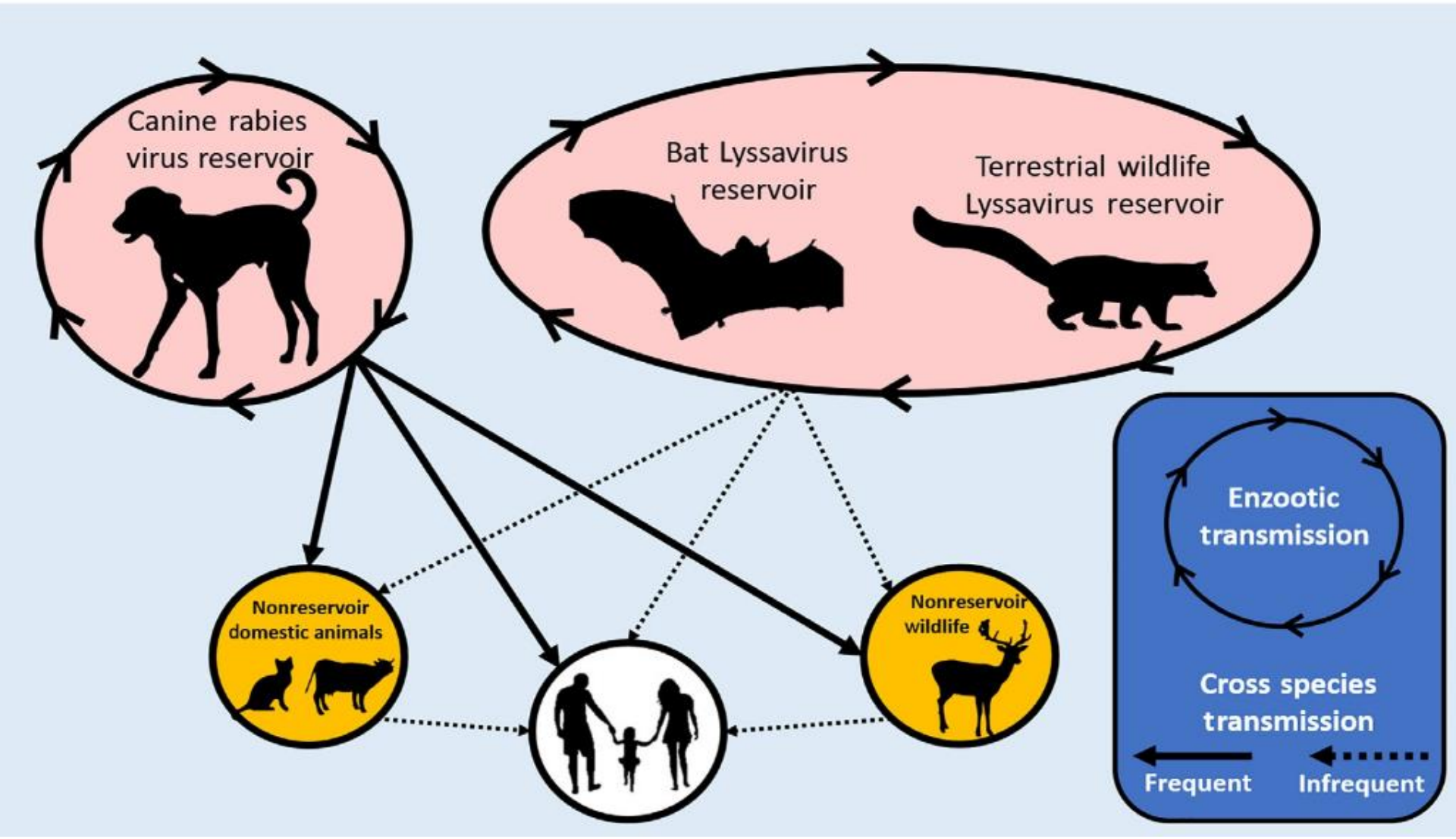
Overall, there are 2 major rabies epidemiological cycles:

- The urban cycle, where the dog is the main reservoir.
- Sylvatic epidemiological cycles:
  - Terrestrial – maintained by terrestrial animals such as foxes, raccoons, and other wild carnivores.
  - Aerial – maintained by bats.

Cycles épidémiologiques de la rage

Monde





Enzootic and cross-species transmission pathways for Lyssavirus species.

Urban cycle:

- In the urban cycle, dogs are the main reservoir and vector of the virus.
- This cycle predominates in certain regions of Africa, Asia, and Central and South America where the proportion of unvaccinated, semi-domestic, or stray dogs is high.
- It has been practically eradicated in North America and Europe; although sporadic cases occur in dogs infected by wild animals.

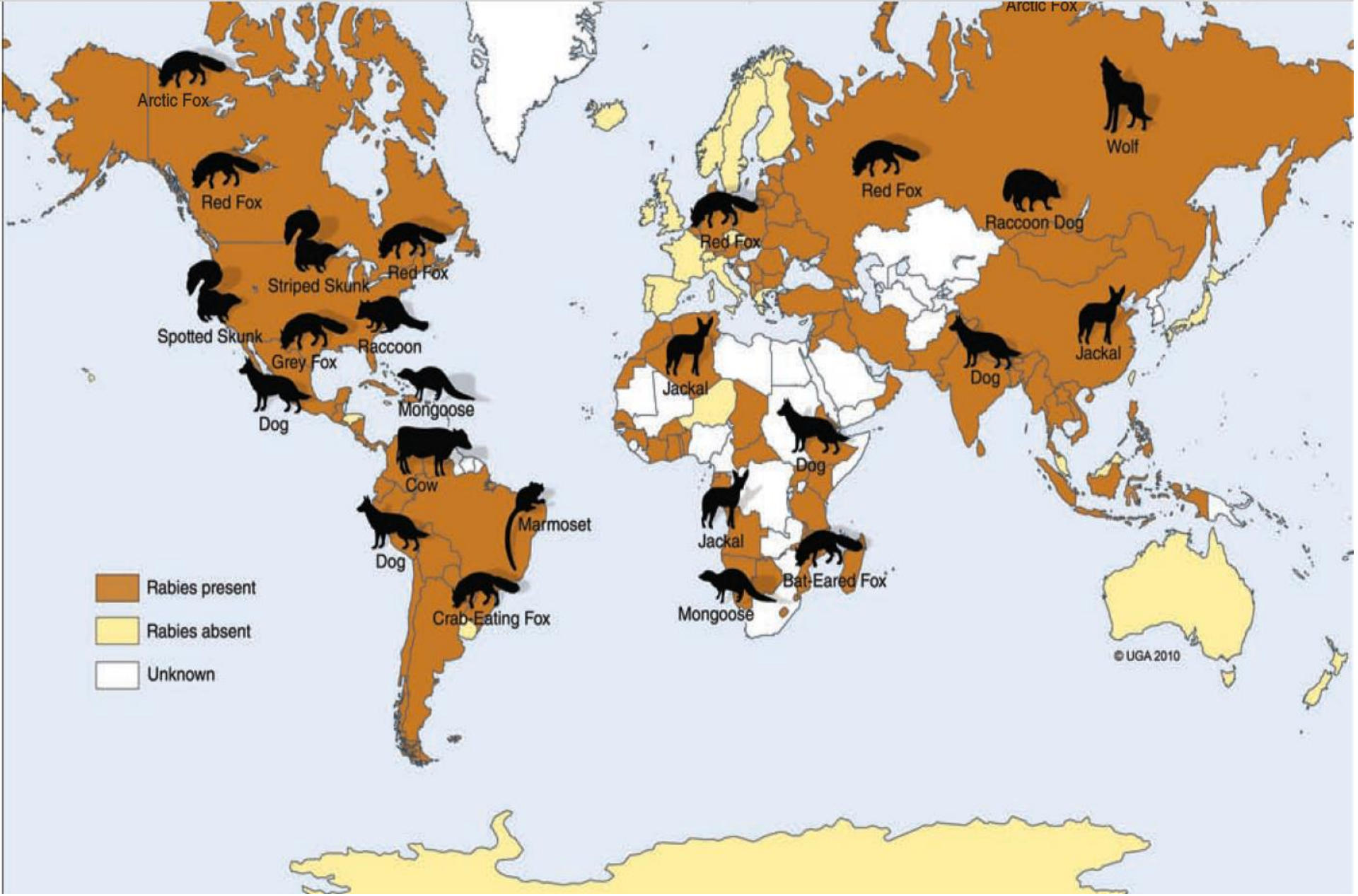
- Represents the leading cause of human mortality due to rabies worldwide, particularly in Asia and Africa

Dog bites and scratches account for 99% of human rabies cases (WHO)

➢ ***Sylvatic cycle - Terrestrial (wild fauna):***

- This cycle is maintained by reservoirs of wild animals.
- The main reservoirs vary by region:

- *North America: Raccoons, skunks, foxes.*
- Latin America: Marmosets (or capuchins), etc.
- *Europe: The raccoon dogs and red fox were the main reservoirs before rabies control efforts (mass bait vaccination of foxes).*
- *Africa and Asia: Jackals, mongooses, and other wild canids.*



Principal animal vectors of rabies for major regions of the world. Some countries are reportedly free of rabies.

Red fox
(Renard roux)

Algerian red fox

- Despite the high prevalence of raccoon rabies in the eastern United States, the only human death associated with a variant of raccoon rabies was reported in 2003.

Aerial cycle or Bat Rage (vampires, frugivorous and insectivorous bats)

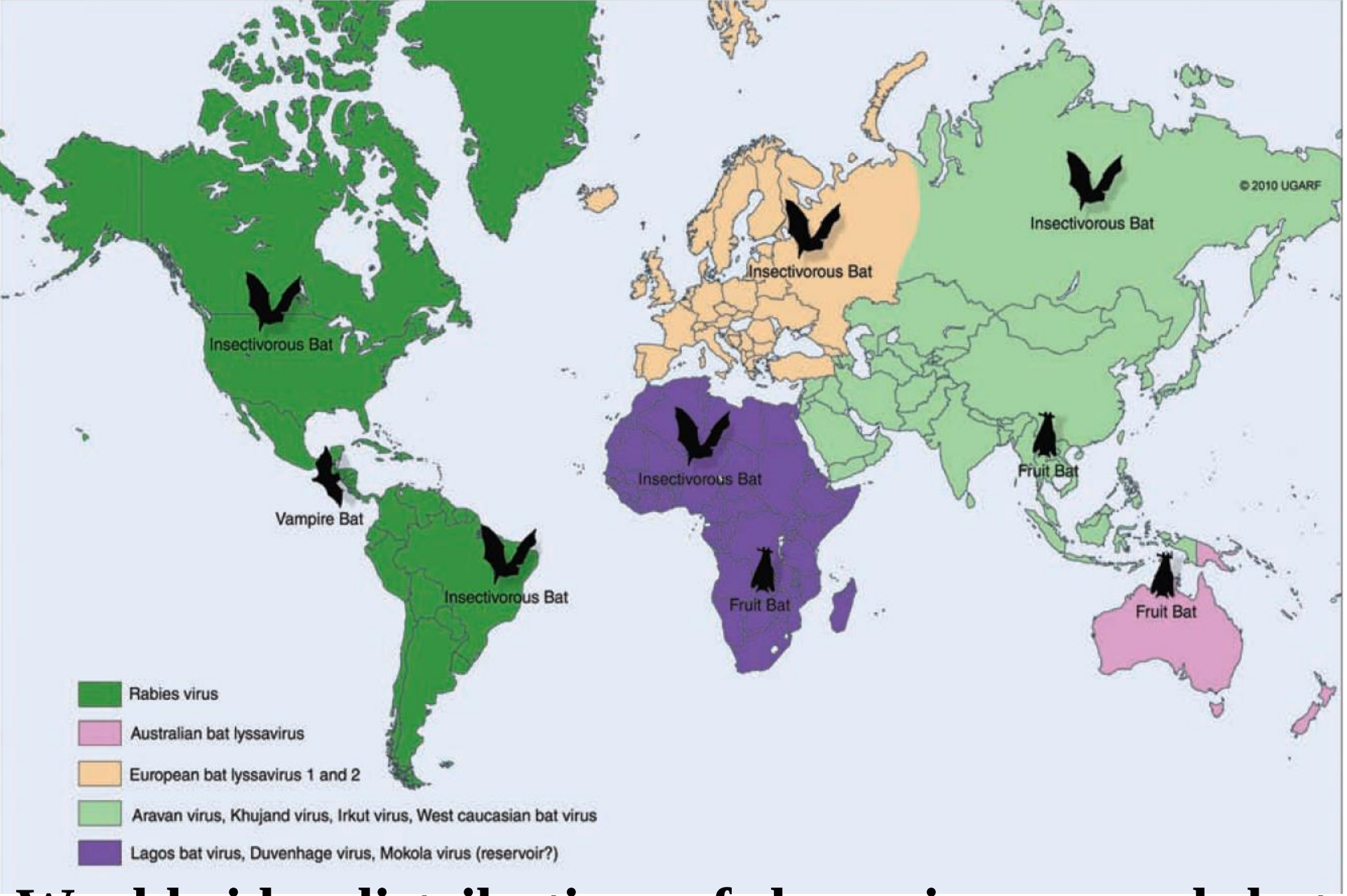
- Often considered a subset of the sylvatic cycle; bats are the main reservoir for most lyssaviruses.
- Unlike terrestrial mammals, bats can sometimes survive infection, but they generally die once clinical symptoms appear.

- Concerns both Americas, Northern and Eastern Europe, Spain, Portugal, and France.
- *Latin America: Vampire bats (Desmodus rotundus) play an important role = often transmitting the virus to livestock.*
- United States: Most humans become infected as a result of contact with insectivorous bats.

- Depending on the species of bats, about 5 to 40% of dead or sick bats tested are infected with the rabies virus.

Bats

Flying foxes



Worldwide distribution of lyssaviruses and bat reservoirs

Rabies annual cases all species combined-Algeria.

Year	Canine (dog)	Bovine	Caprine/Ovine	Feline	Equide	Other	Overall
2006	495	221	89	37	85	9	936
2007	636	244	105	42	79	7	1113
2008	715	203	121	49	110	14	1212
2009	432	217	61	20	35	16	781
2010	302	137	72	34	58	12	652
2011	381	242	90	38	48	08	807
2012	407	219	63	22	61	17	789
2013	375	198	74	24	32	11	714
Mean	467.875	210.125	84.375	33.25	63.5	11.75	875.5

Public health

- Each year, about 60,000 people die from rabies worldwide.
- About half of these deaths occur in India.
- It is estimated that 3 billion people remain at risk of infection from the rabies virus in more than 100 countries.
- A large portion of these individuals are children who are victims of dog bites from rabid dogs.
- In the United States, the number of human deaths due to rabies has decreased from over 100 per year in the early 20th century to 2 or 3 per year.

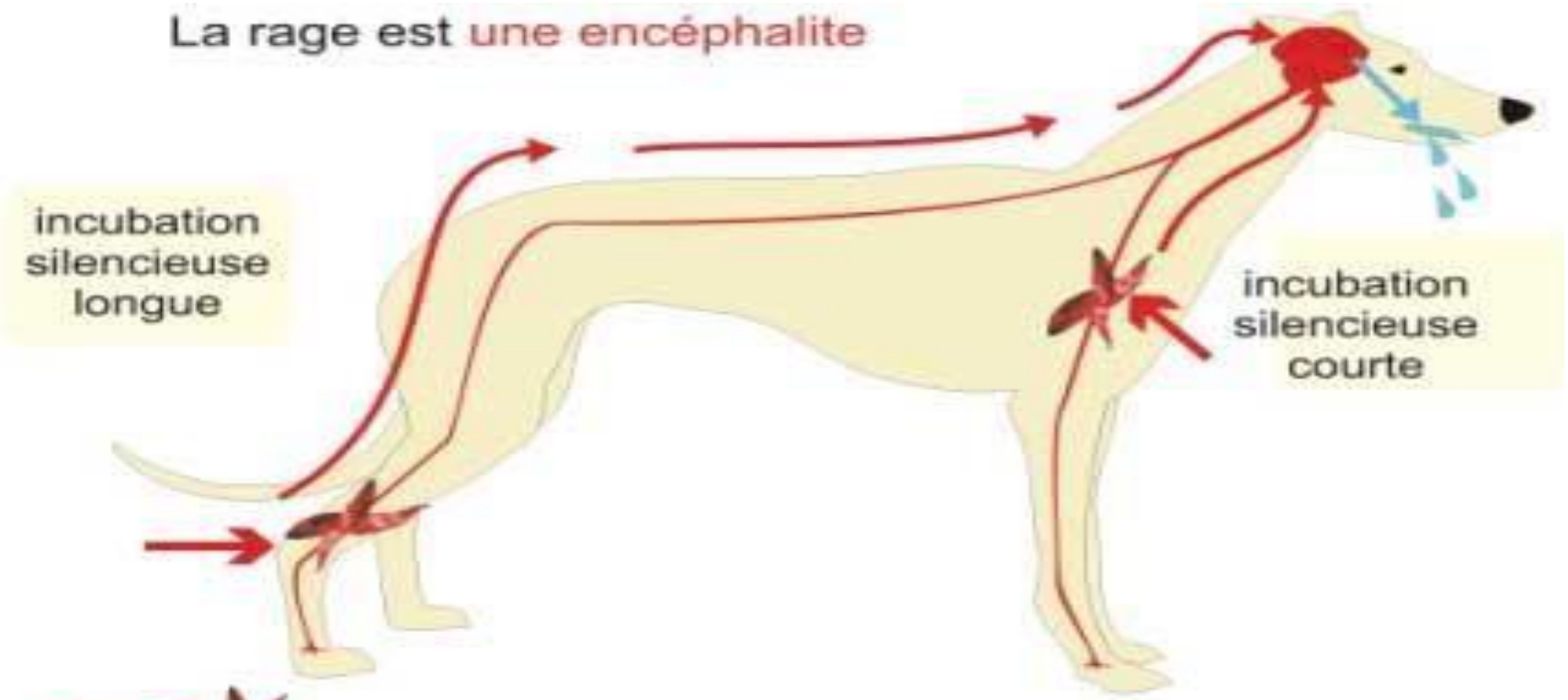
The annual human rabies death and (PEP) in Algeria

Years	Number of PEP cases	PEP from history of domestic dog bite (%)	PEP from history of stray dog bite (%)	PEP from other animals' bite	Death from Rabies human (male)
2006	47,583	21,412 (45%)	26,150 (5(%)	21(<0.01%)	11 (14)
2007	76,765	23,025 (30%)	55,714 (70%)	26(<0.01%)	24 (24)
2008	74,321	24,525 (33%)	41,773 (6è%)	23(<0.01%)	25 (25)
2009	75,988	15,179 (20%)	60,759 (80%)	32(<0.01%)	12 (12)
2010	88,966	28,689 (30%)	60,252 (70%)	25(<0.01%)	13 (13)
2011	97,321	39,387 (38%)	57,903 (6é%)	31(<0.01%)	16 (16)
2012	109,811	35,934 (20%)	73,849 (80%)	28(<0.01%)	17 (17)
2013	114,652	39,672 (31%)	74,690 (69%)	20(<0.01%)	15 (15)

Pathogenesis of rabies

- The incubation period is generally 3 to 12 weeks, but can vary from a few days to several months, rarely exceeding 6 months. It depends on:
  - Viral multiplication at the entry site.
  - Viral dose.
  - Inoculation site.
- Transport via Axonal pathways.
- Neuronal multiplication: CNS.
- Multiplication in the salivary glands.

La rage est une encéphalite



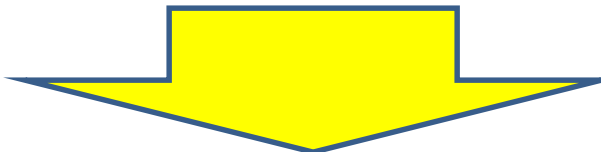
Morsure contaminante, multiplication locale du virus

Infection centripète des neurones vers le cerveau

Infection centrifuge vers les glandes salivaires (le sujet devient excréteur du virus)

incubation silencieuse 1 à 2 mois	maximum 14 jours	signes cliniques
	salive contaminante	

- After inoculation in subcutaneous tissues and muscles, the rabies virus replicates locally in muscle cells, then binds to peripheral nerve endings.
- Local replication around the bite site can continue for months before the virus reaches peripheral sensory and motor nerve endings.
- The nicotinic acetylcholine receptor being its main receptor.

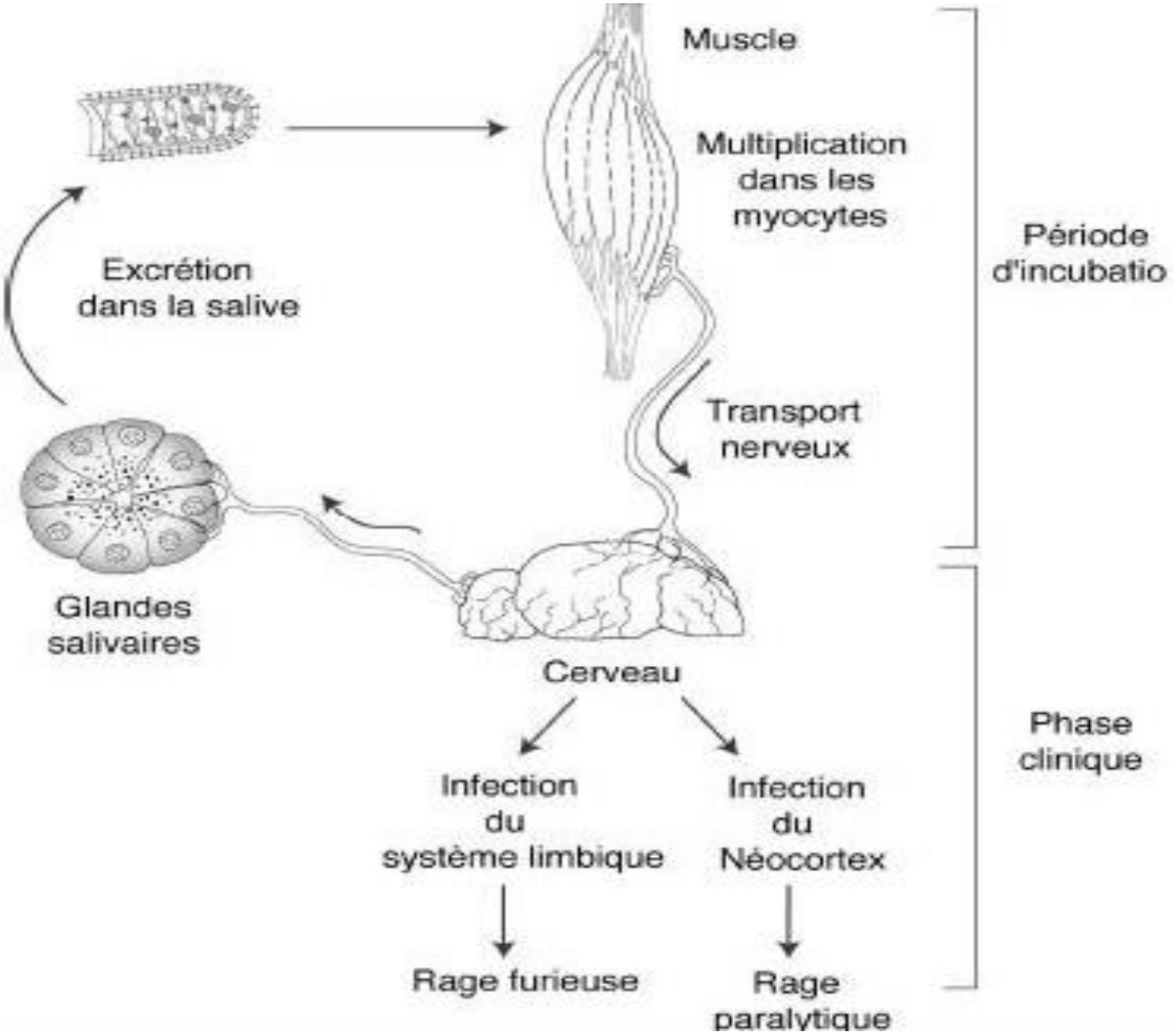


1- Centripetal phase

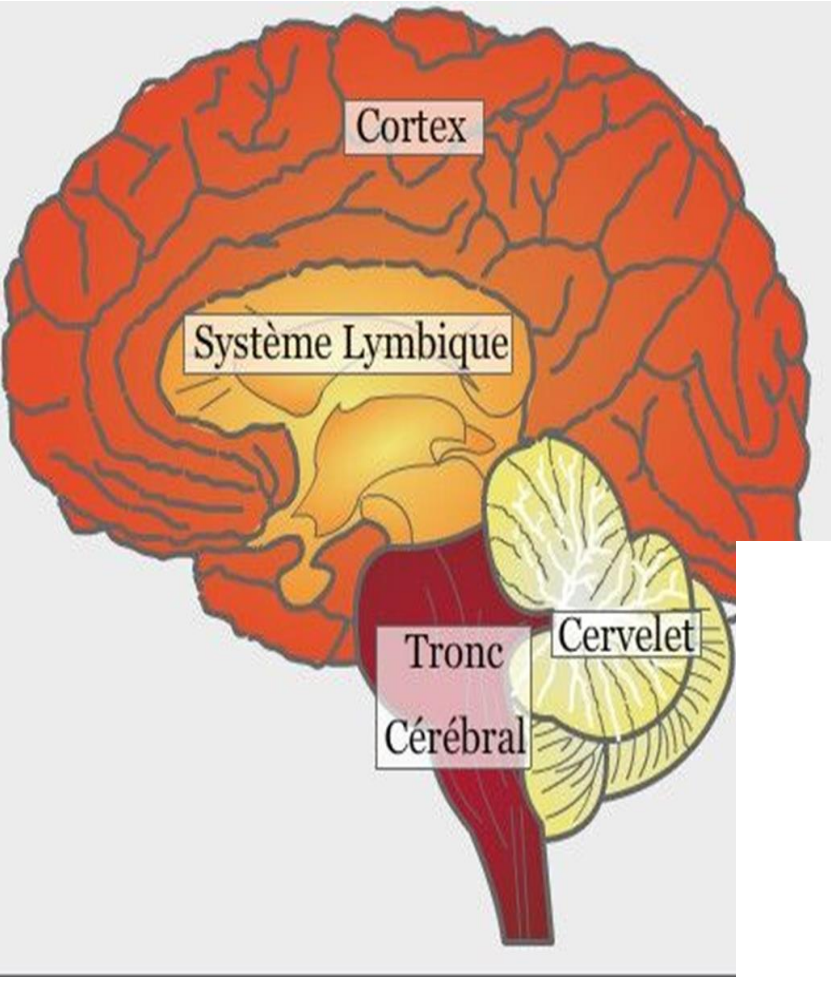
- The virus then retrogradely travels along the axons at a speed of 3 mm/h.
- Once in the CNS, it replicates massively, with intercellular transmission of the virus through synaptic junctions.
- The spinal cord, medulla oblongata, periaqueductal gray matter, limbic system, and cerebellum are particularly affected.

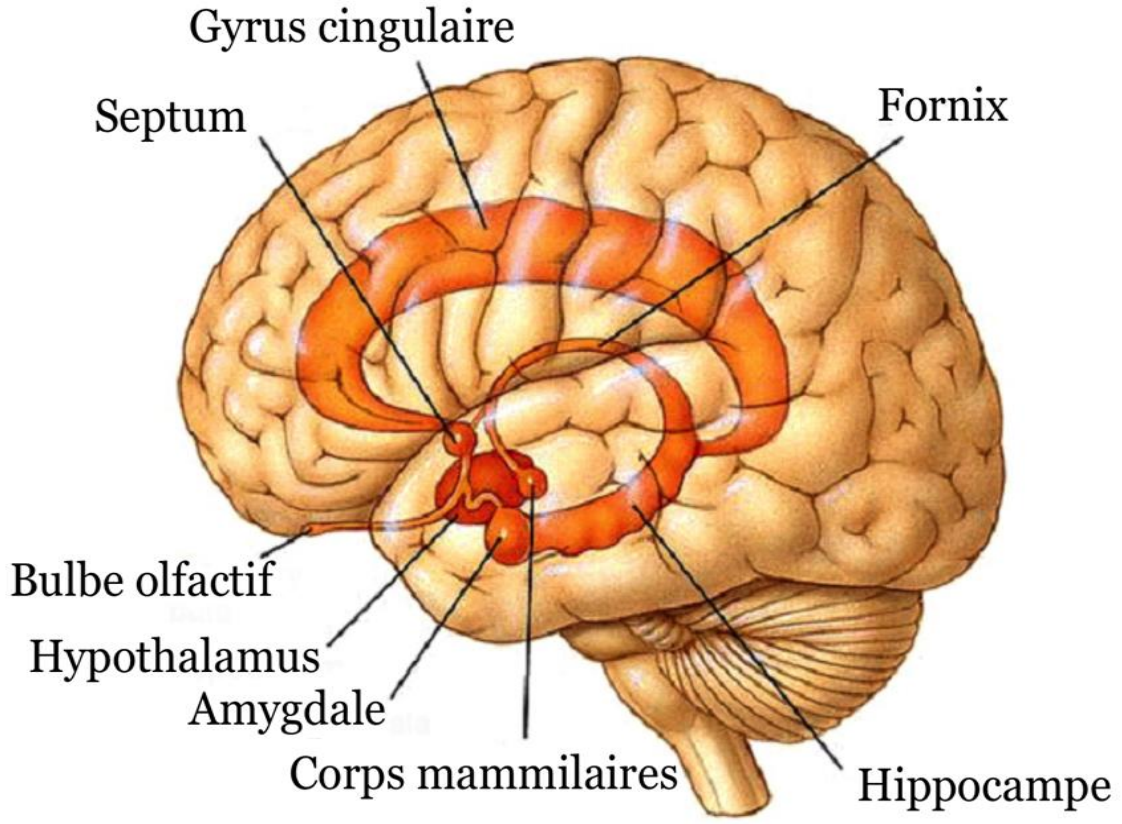
2- Centrifugal phase

- The virus spreads out of the CNS through somatic and autonomic nerves and settles in various tissues, including cardiac and skeletal muscles, the eye, the kidney, the pancreas, peri-follicular nerves, and salivary glands.
- The production of new virions mainly occurs in the salivary glands.
- Thus, the presence of the virus in saliva indicates an infection of the CNS.
- In some animals, death occurs before saliva becomes infectious.
- In some dogs, the virus is excreted up to 13 days before the onset of clinical signs.


Muscle
Multiplication dans les myocytes
Période d'incubatio
Excrétion dans la salive
Transport nerveux
Glandes salivaires
Cerveau
Phase clinique
Infection du système limbique
Infection du Néocortex
Rage furieuse
Rage paralytique

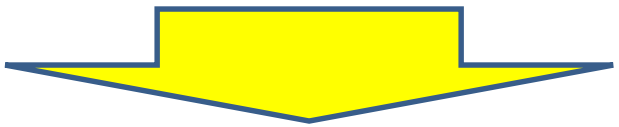
Limbic system





Clinical study

- Not all bites from a rabid animal necessarily lead to rabies.
- The infection is not always fatal, except in cases where clinical signs appear.
- In the absence of Post-Exposure Prophylaxis (PEP) treatment: up to 60% of people bitten on the head or neck by a rabid dog develop rabies, compared to up to 40% for those bitten on the hand and 10% for those bitten on the trunk or leg.

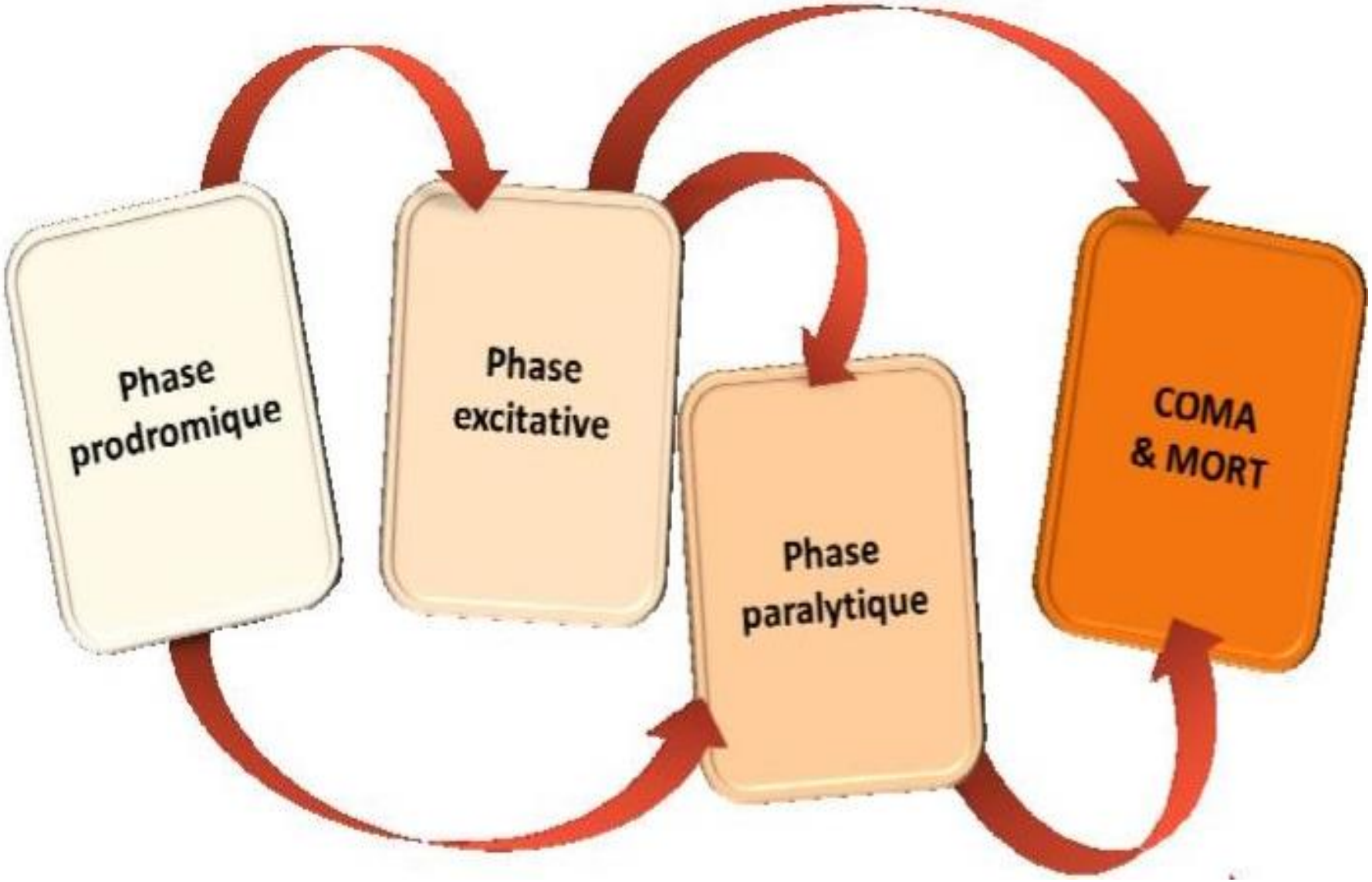


Among the factors influencing the progression of the disease after a bite are:

- The proximity of the bite site to the central nervous system (CNS).
- The degree of innervation of this site.
- The age of the host (young animals being more vulnerable).
- The amount of virus inoculated.
- The neuroinvasive power of the variant of the rabies virus in question.

❖ ***Clinical signs (dog and cat)***

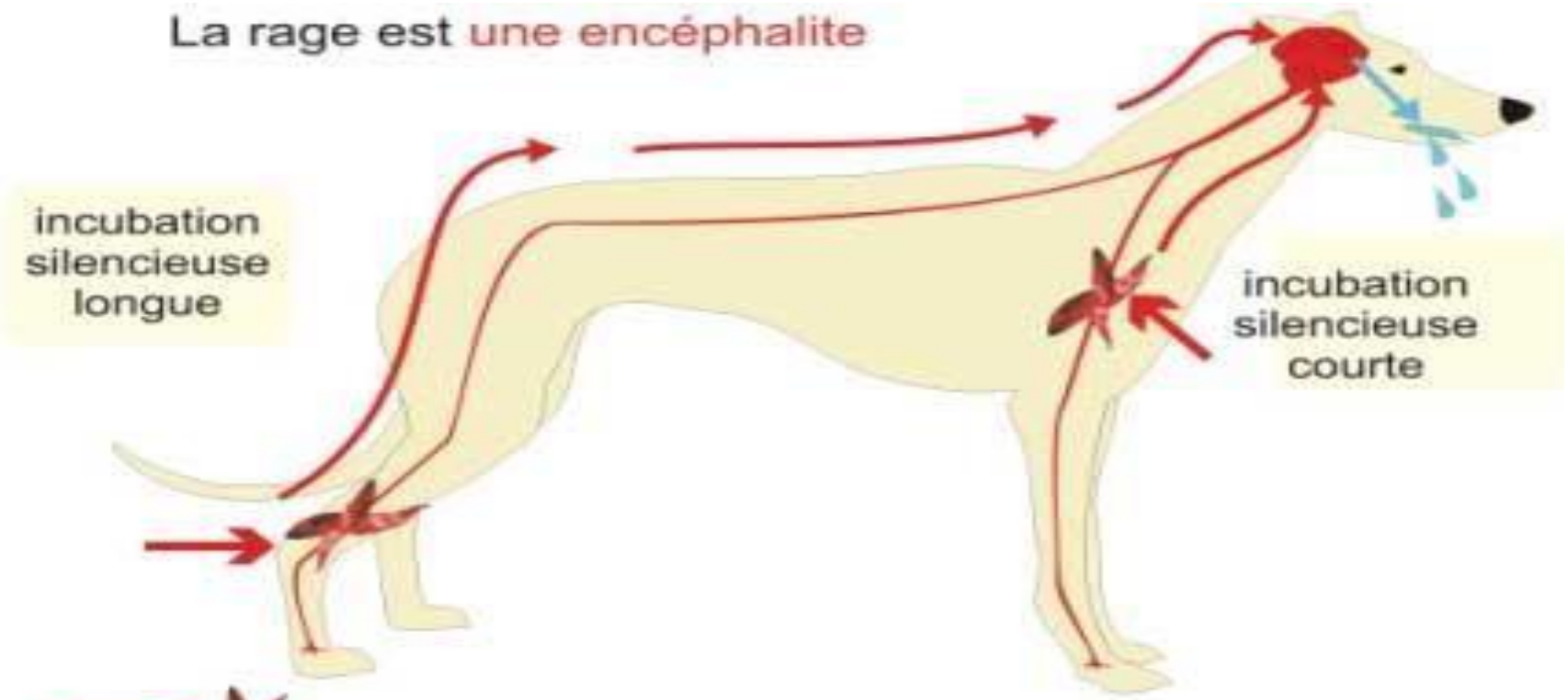
- There are no characteristic symptoms: "everything is rabies and nothing is rabies."
- The clinical evolution, although variable, is classically divided into 3 phases: prodromal, furious (excitatory), and paralytic.
- Death usually occurs between 3 and 10 days after the appearance of the first signs.
- However, some animals exhibit atypical rabies and do not develop these stages.


Phase prodromique
Phase excitative
Phase paralytique
COMA & MORT

Incubation

- Incubation period = 1 week - 6 months.
- Most dogs and cats develop the disease = 1 to 2 months after exposure; Extremes = 5 days to 6 years.
- The closer the bite site is to the CNS, the shorter the incubation period.
- Also influenced by the host species, age, the degree of innervation at the bite site, the neuroinvasiveness of the rabies virus variant, and the amount of virus inoculated.
- Although 90% of humans develop the disease within 6 months of exposure, incubation periods of 6 years or more have been reported.

La rage est une encéphalite



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incubation silencieuse 1 à 2 mois	maximum 14 jours	signes cliniques
	salive contaminante	

- Clinical signs often include a sudden change in behavior and progressive paralysis.
- Rabies can manifest clinically in two forms:
  - Furious form: Young animals may also present this form of rabies.
  - Dumb or paralytic form.

Furious form

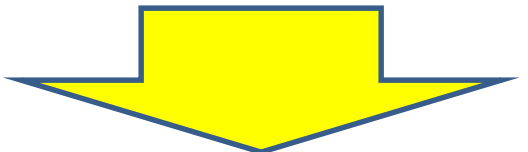
Prodromal phase (1 to 3 days)

- When it occurs, the prodromal phase lasts 2 to 3 days in dogs and 1 to 2 days in cats.
- Often goes unnoticed, but subtle signs may appear:
- Variable intensity fever, excessive licking, or biting in the bite area (related to itching).

- Behavior changes = Erratic behavior: Dogs and cats may become lethargic, anorexic, anxious (fearful), agitated, or withdrawn (trying to hide in dark and quiet places); some animals become more docile or affectionate; vomiting may occur.
- Slowing of corneal and eyelid reflexes.
- Myosis, or sometimes reduced photomotor reflexes.

Furious phase (or excitatory)

- Occurs in about two-thirds of affected cats and dogs and lasts from 0 to 7 days.
- Initially, the anterior region of the CNS brain (forebrain) is invaded, resulting in signs of erratic and unusual behaviors = Irritability, excitability, agitation, anxiety, hyperesthesia, hypersalivation, vocalizations (barking, meowing), unexplained wandering, pronounced aggressiveness, pica, and abnormal sexual behavior.



- *Irritability, excitability, agitation: The animal reacts excessively to visual and auditory stimuli with photophobia, hyperesthesia.*
- *Aggressiveness: Spontaneous and/or episodic = The animal may attack and bite other animals, people, or even objects (biting objects, cages, moving objects, etc.).*
- *Pica: Affected animals may attempt to ingest foreign bodies, which can lodge in their digestive tract.*

- Some animals develop ataxia, disorientation, tremors, vestibular disorders, and generalized tonic-clonic seizures (during which they may die).

A dog with rabies. Note the slightly dropped jaw, excessive salivation, and manic look.

Dog demonstrating aggressive behaviour resulting from rabies.

- In cats:

- Tremors, a fixed, distracted, worrying, or frightening look, and increased vocalizations can be observed.

- Behavior change:

- Extreme agitation and hyper-reactivity to external stimuli, disorientation, aimless wandering (compulsive running).

- These animals often develop aggressive behaviour.

Paralytic phase

- Develops 1 to 10 days after the onset of clinical signs.
- A progressive lower motor neuron type paralysis develops, causing signs of ascending paresis or paralysis of the limbs (often initially affecting the bitten limb).
- The neurological examination reveals flaccid paralysis with abolition of spinal reflexes and signs of cranial nerve paralysis.

- Signs of cranial nerve paralysis:

- Laryngeal paralysis: May lead to dyspnea, voice disturbance (dysphonia) = change in the pitch of the dog's bark or the cat's meow.
- Pharyngeal muscle paralysis: Hypersalivation, hydrophobia, dysphagia, etc.
- Masticatory muscle paralysis: 'Dropped jaw' may occur due to paralysis of the masticatory muscles, especially in dogs.

- If euthanasia is not performed, coma and death generally occur within a week following the onset of symptoms =

  Death in 2 to 10 days. 5 days on average.
- Death is associated with multiorgan failure, particularly cardiac and respiratory.
- Recovery from rabies is extremely rare (experimentally, some dogs have recovered from clinical rabies several days, or even months, after being infected with certain strains of the rabies virus).

A feral dog with end-stage rabies.

Major Clinical Findings in 183 Cats and 119 Dogs with Rabies in the United States

Sign	Percent of Cats	Percent of Dogs
Aggression	55	31
Ataxia	30	49
Irritability	34	23
Anorexia	22	38
Lethargy	20	37
Hypersalivation	14	41
Dysphagia	10	30
Lameness	18	16
Limb paralysis	17	29
Jaw paralysis	3	29
Dysphonia	16	9
Hyperesthesia	10	17
Seizures	8	14
Fever	3	14

Silent or paralytic form

- Infected animals show lethargy, limb paralysis, ataxia, and excessive salivation due to their difficulty swallowing.
- Hydrophobia: Some animals avoid drinking or are afraid of water.
- Dogs can often have paralysis of the masticatory muscles: 'Dropped jaw.'
- Infected animals develop progressive paralysis and then die.
- Animals presenting this form of rabies may also be confused with other diseases such as distemper.

Atypical rabies = Asymptomatic carriers

- Some animals develop subclinical, chronic, or resolved infections, unlike typical furious and paralytic forms.
- This phenomenon has been observed in dogs, cats, bats, and skunks.
- These animals can survive and excrete the virus for long periods.
- Example: In endemic areas (for example, in Africa), dogs can carry the rabies virus and excrete it in their saliva without showing clinical signs.

❖ ***In humans***

- The prodromal signs of rabies in humans include malaise, fever and pain, itching or paresthesias at the site of inoculation.
- People with furious rabies become nervous and hyperexcitable, after which signs of hydrophobia, aerophobia, confusion, and aggression develop.
- Autonomic signs such as hypersalivation, vomiting, miosis or mydriasis, excessive sweating, etc., may occur.
- Paralytic rabies can be confused with Guillain-Barré syndrome.

Diagnosis
(dog and cat)

- Rabies should be suspected in dogs and cats showing a sudden onset of behavioral changes, flaccid paralysis, or other unexplained neurological signs, especially in regions of rabies enzootics or in animals imported from countries where rabies is endemic.
- Although increased vigilance is warranted for animals not vaccinated against rabies, cases have been reported in partially or fully vaccinated dogs and cats; therefore, a history of rabies vaccination should not rule out rabies.

D'une façon générale, en région d'enzootie rabique ou sur un animal en provenant :

- **Toute modification du comportement habituel d'un animal** (agressivité inhabituelle, abattement excessif...),
- **Toute gêne de la mastication ou de la déglutition**,

doit être considérée comme un élément de suspicion de la rage.

Differential diagnosis:

- Any neurological disease = Canine distemper (absence of hypersalivation; multisystemic signs), toxoplasmosis, neosporosis, pseudorabies (absence of intense pruritus in cases of rabies), poisonings (organophosphates, lead, strychnine, inorganic arsenic), neoplasms, granulomatous meningoencephalitis (GME), polyradiculoneuritis, hepatic encephalopathy, and cranial trauma.
- Other causes of laryngeal paralysis,

Laboratory abnormalities:

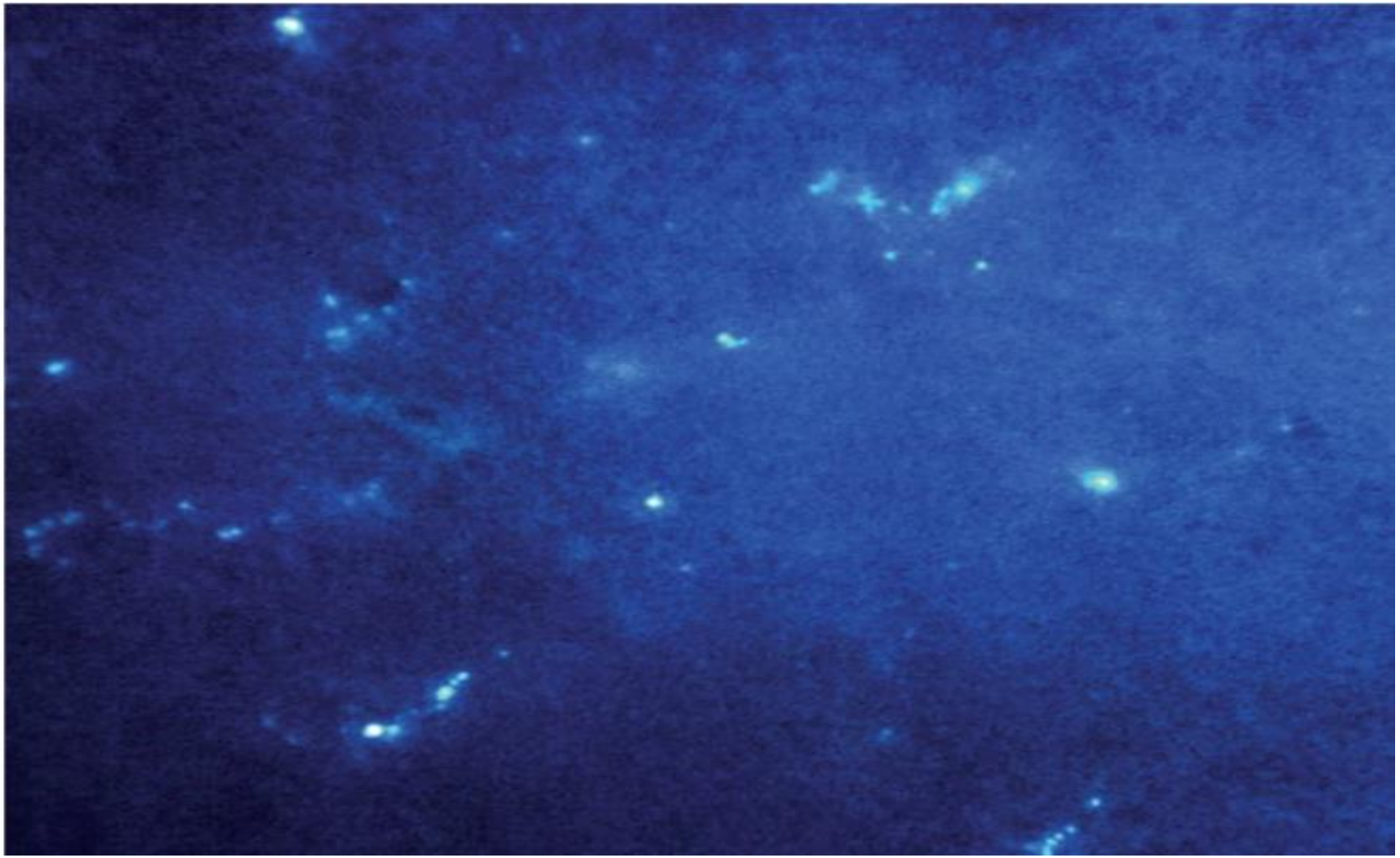
- Complete blood count, blood biochemical profile, and urinalysis: no characteristic abnormalities.
- Cerebrospinal fluid (CSF): A slight increase in protein and leukocyte levels may be observed.

Microbiological analyses (dog and cat):

1. Direct fluorescent antibody staining (DFA) or immunohistochemistry:

- Samples: Brain, spinal cord, saliva, skin biopsies (the latter not recommended in animals), other extra-cranial tissues (tongue, salivary glands, adrenal glands, pancreas, digestive tract, and myocardium).
- Target: Protein N of the rabies virus.

- High sensitivity and specificity on brain tissue.
- Sensitivity on extracranial tissues is relatively low.
- A negative result does not exclude rabies; confirmatory tests such as mouse inoculation or RT-PCR are required for negative samples.
- Ante-mortem detection of rabies antigens in skin biopsies; however, a high percentage of false negatives limits the usefulness of this skin test.



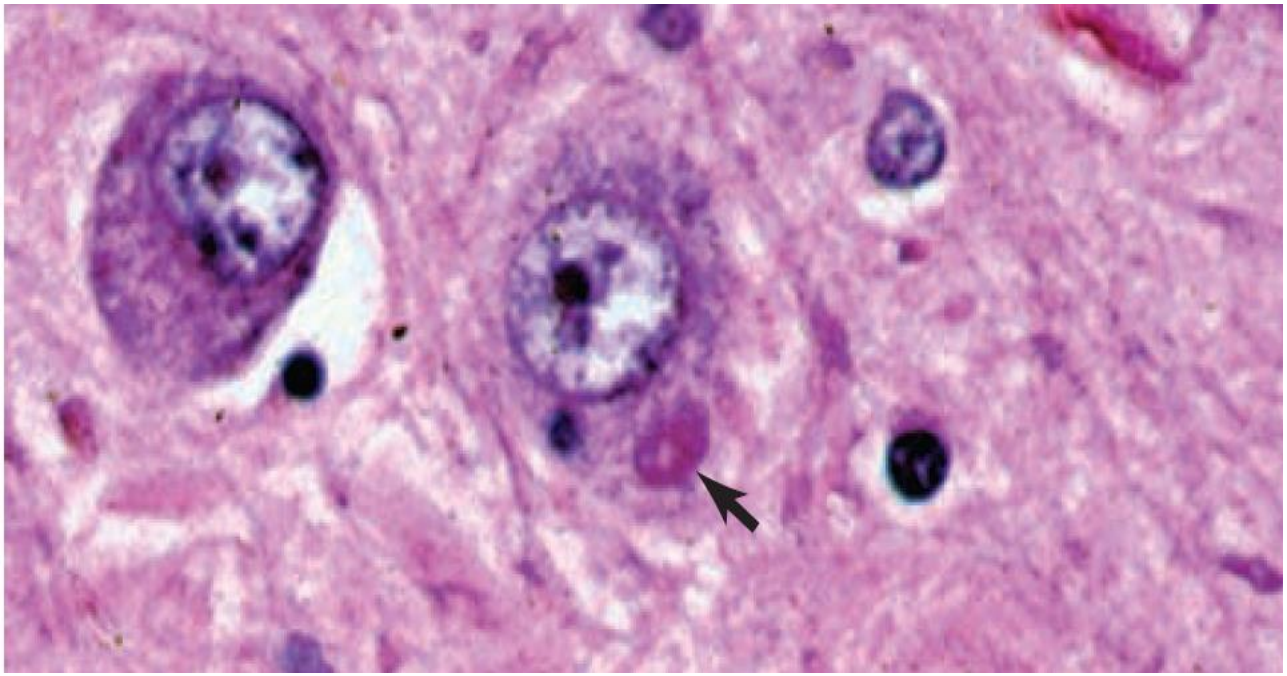
Direct immunofluorescence microscopy showing the presence of the rabies virus antigen in the brain tissue of a fox.

2. Serology:

- Samples: Serum or CSF.
- Target: Anti-rabies antibodies.
- Viral neutralization tests are the reference method in serology, although ELISA tests are also available.
- Rarely useful for the diagnosis of rabies, as the immune response is delayed and antibody titers are therefore often negative.
- In dogs and cats, serological tests are most often used to attest to prior vaccination, which is mandatory for the importation of animals into rabies-free countries.

3. Histopathology:

- **Samples: Brain, spinal cord.**
- Target: Intracytoplasmic eosinophilic inclusions (Negri bodies).
- The detection of Negri bodies has a low sensitivity (observed in 70%-80% of rabies cases).



Negri body (arrow) in a neuron within the CNS (H & E stain, × 400).

4. RT-PCR:

- Samples: Brain, spinal cord, saliva, CSF, extracranial tissues;
- Target: RNA of the rabies virus.
- Fast (in a few hours).
- Potentially very sensitive and specific.
- Can be used to identify genotypes and strains of rabies viruses.

Note:

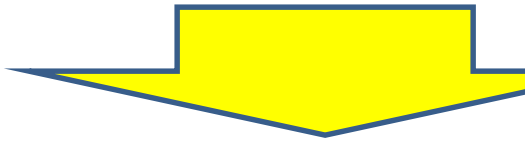
- Samples must be taken with great care to avoid contamination during decerebration.
- Samples must be accompanied by detailed memorials.
- Fresh frozen tissues (not fixed) are preferred for rabies diagnosis.

Treatment and prognosis

- Rabies invariably leads to death in pets within 1 to 10 days after the onset of symptoms.
- Under no circumstances should first aid be attempted on a dog or cat suspected of having rabies.
- Once rabies is strongly suspected in a dog or cat, euthanasia is justified, followed by the sending of the brain for analysis.

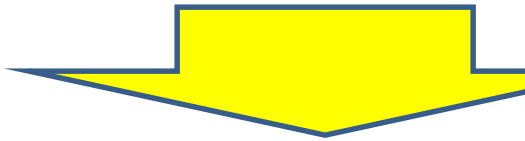
- Once clinical signs appear, rabies is almost always fatal and very few people have survived it.
- A very small number of people have survived, with about 30 to 31 documented and recorded cases in the scientific literature up to 2023.
- However, the majority of survivors suffer from neurological sequelae.
- Most victims were children, several of whom had been vaccinated against rabies before the onset of symptoms.

- After treatment with artificial coma (Milwaukee protocol), an 8-year-old girl survived rabies, likely contracted after being scratched by a stray cat.
- In rare cases, dogs that received an experimental injection of certain variants of the rabies virus have recovered from rabies encephalitis, with intermittent shedding of the virus in saliva after recovery.



In humans; different therapies are attempted:

- Milwaukee protocol: Involves the induction of coma and administration of antivirals.
- Specific ones like the administration of rabies serum.
- Non-specific measures such as interferon injection, hospitalization in intensive care, etc.



Prevention

Prevention in dogs and cats

The prevention of rabies relies on the following measures:

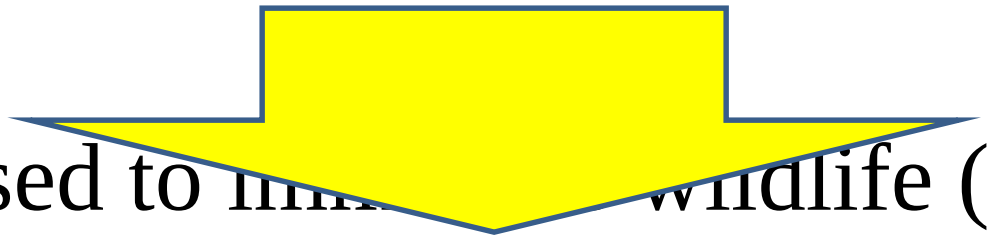
- Raising public awareness of the need to vaccinate dogs and cats (and ferrets) against rabies = Vaccination of dogs and cats is a very effective measure.
- Subsidized programs have allowed for the vaccination of the largest number of pets in developing countries where rabies is endemic.
- Wildlife vaccination programs.

- Raising public awareness of the risks associated with contact with wildlife = The possession and importation of wild and hybrid animals is discouraged.
- Control of stray dogs and cats.
- It is imperative to avoid any contact between domestic animals and wildlife.
- If contact is required (hunting dog for example) = Puppies and kittens that have not yet reached the age for rabies vaccination must be kept away from wildlife.

Vaccination

- The most commonly administered rabies vaccines for dogs and cats are those based on inactivated virus.
- There are also recombinant rabies vaccines (intended for cats) using Canarypox virus as a vector.
- Modified live rabies vaccines are not permitted in many countries, including Algeria, due to occasional cases of post-vaccinal rabies encephalitis in dogs and cats.

- Recombinant rabies vaccines with glycoprotein (G) and vaccine vector (usually an adenovirus) are next-generation vaccines that trigger immunity without causing disease =



Generally used to immunize wildlife (fox for example)

Note: It is not recommended to own wild animals; no parenteral vaccine is approved.

- An effective vaccination rate of at least 70% of the dog population is necessary to prevent rabies epizootics.
- All dogs and cats must be vaccinated against rabies.
  - Primary vaccination = At the age of 3 or 4 months (depending on the legislation in force).
  - A booster dose one year later.
  - Then every 3 years with approved inactivated vaccines, or annually with recombinant vaccines (cat).
- Ferrets can be vaccinated at the age of 3 months and revaccinated annually with an approved vaccine.

Guidelines for Vaccination of Individual Pet Dogs

Vaccine	Initial Vaccination		Booster Schedule	Comments
	Age ≤ 16 Weeks	Age > 16 Weeks		
Rabies (I, SC)	One dose as early as 3 months of age depending on local regulations	Single dose	1 year, then every 3 years thereafter with an approved product for 3-yearly immunization. Local regulations may dictate alternate protocols.	*Core.* In endemic areas or where required by local regulations

Guidelines for Vaccination of Dogs in Shelter Environments

Vaccine	Initial Vaccination		Recommendations for Booster at Exit	Comments
	Age ≤ 16 Weeks	Age > 16 Weeks		
Rabies (I, SC)	If at all, one dose on exit from the shelter as early as 3 months depending on local regulations	If at all, one dose on exit from the shelter	1 year, then every 3 years thereafter with an approved product for 3-yearly immunization. Local regulations may dictate alternate protocols.	Use in endemic areas. Local regulations can dictate the need for rabies immunization.

I, inactivated whole organism; SC, subcutaneous.

Guidelines for Vaccination of Individual Pet Cats

Vaccine	Initial Vaccination: Age ≤ 16 Weeks	Initial Vaccination: Age > 16 Weeks	Booster Schedule	Comments
Rabies (I, SC)	One dose as early as 3 months of age depending on local regulations	Single dose	1 year, then every 3 years thereafter with an approved product for 3-yearly immunization. Local regulations may dictate alternate protocols.	Core in endemic areas or where required by local regulations. Provides strong protection. Vaccine-associated sarcoma task force recommended immunization as distal as possible in the right pelvic limb.
Rabies (recombinant canarypox, SC)	Single dose as early as 8 weeks of age depending on local regulations	Single dose	Annual	Core in endemic areas or where required by local regulations. Provides strong protection. Vaccine-associated sarcoma task force recommended administration as distal as possible in the right pelvic limb

Guidelines for Vaccination of Cats in Shelter Environments

Vaccine	Initial Vaccination: Age ≤ 16 Weeks	Initial Vaccination: Age > 16 Weeks	Recommendations for Booster at Exit	Comments
Rabies (I, SC)	If at all, one dose on exit from the shelter as early as 3 months depending on local regulations	If at all, one dose on exit from the shelter	1 year, then every 3 years thereafter with an approved product for 3-yearly immunization. Local regulations may dictate alternate protocols.	For use in endemic areas. Local regulations may dictate the need for rabies immunization.

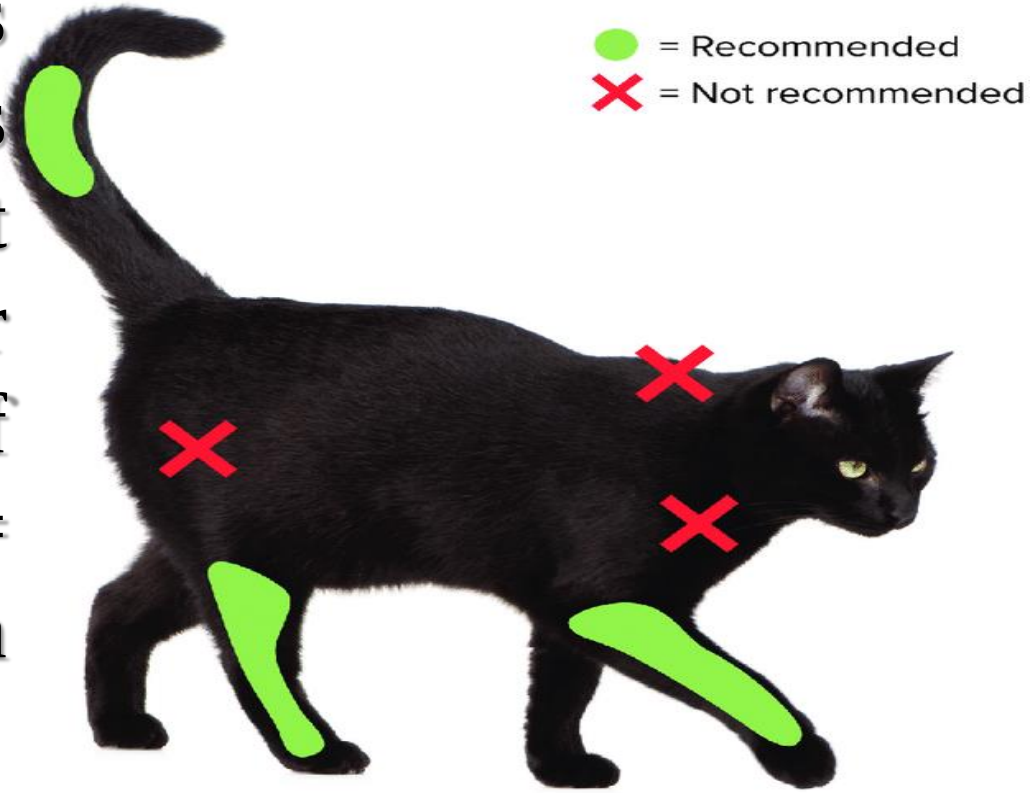
I, inactivated whole organism; SC, subcutaneous.

- **Canine rabies vaccination is mandatory in many countries, including Algeria, and must be administered exclusively by a veterinarian (or under their direct supervision).**
- In the United States: Owners who do not comply with state or local requirements must be reported to health authorities.
- Although rare, rabies has been reported in vaccinated animals, particularly when their vaccinations are not up to date.

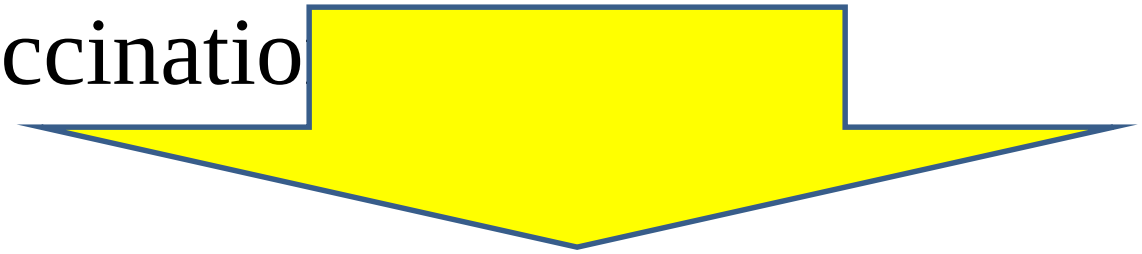
- Dogs and cats: Immunity is not fully developed until 28 days after the initial rabies vaccination (primary vaccination). Due to a rapid immune response, the vaccinated animal is considered fully immunized immediately after the rabies booster.
- Most often, vaccination against the rabies virus is associated with = Pain at the injection site, lameness, transient fever, local skin reactions (alopecia, focal cutaneous vasculitis, subcutaneous granuloma).

- The use of inactivated rabies vaccines in cats has been associated with the formation of sarcomas at the injection sites (rare in cats; rarer in dogs).

Administer the rabies vaccine as distally as possible in the right pelvic limb, to allow for complete excision of sarcomas (amputation) = less recommended in dogs).



- Generalized ischemic dermatitis (DIG) in dogs is a rare skin reaction related to rabies vaccinatio



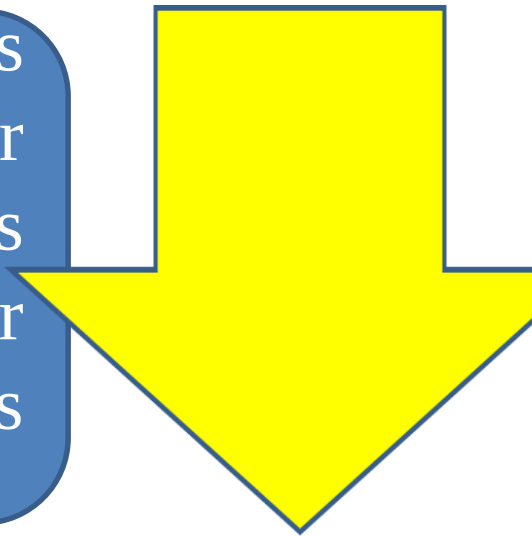
- Variable alopecia, crusts, erosions and ulcers on the ear margins, periocular region, tip of the tail and the pads.

Skin lesions of generalized post-vaccinal ischemic dermatitis in a dog. Swelling of the legs and face with multifocal and symmetrical regional alopecia; facial and appendicular predominance = Digital, facial and peribuccal erosions, with variable-sized crusts, erythema, edema, ulcers and crusts at the level of the ear pavilions.

Post-exposure management in dogs and cats

- Report any human or animal exposure to local health authorities.
- The recommendations regarding dogs and cats exposed to rabies (bite from a rabid animal or wildlife unavailable for testing) are as follows:

Exposure to rabies occurs when the virus is introduced into wounds caused by a bite or scratch, in open wounds or on mucous membranes through saliva or other potentially infectious substances, such as nervous tissue.



Dog or cat exposed to a rabid animal or a wild animal not available for testing:

- *Situation 1 = Unvaccinated dog or cat.*
- *Situation 2 = Outdated booster vaccinations.*
- *Situation 3 = Vaccinated dog or cat*

NB:

- *The duration of quarantine is determined based on the incubation period of rabies.*
- Animals showing signs compatible with rabies during quarantine must be euthanized and tested for rabies.

❖ ***Situation 1 = Unvaccinated dog or cat:***

- Immediate euthanasia is recommended for tissue examination.
- If the owner refuses euthanasia:
  - Place in strict isolation (quarantine in a secured enclosure) for 6 months.
  - Vaccinate during isolation (upon entry for example) or 1 month before release.
  - If symptoms suggesting rabies appear during isolation, immediate euthanasia and a diagnostic test for rabies are necessary.

❖ Situation 2 = Outdated booster vaccinations:

Case-by-case assessment = Contact public health authorities, who determine procedures (revaccination or euthanasia) based on the biting species, local rabies prevalence, and previous vaccination schedules.

❖ Situation 3 = Vaccinated dog or cat:

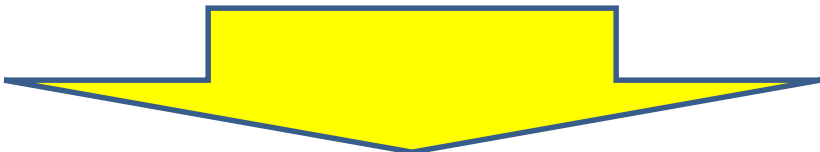
Revaccinate immediately (within 48 hours) and keep under the control and supervision of the owner for 45 days.

Prevention in humans

Pre-Exposure Prophylaxis (PrEP) against rabies

Rabies pre-exposure prophylaxis (PrEP)

- Approximately 15% of untreated individuals after a bite from a rabid animal contract rabies.
- Once symptoms appear, rabies is almost always fatal; therefore, prevention is essential = Rabies pre-exposure prophylaxis (PrEP)
- **Rabies PrEP is a preventive vaccination aimed at individuals at high risk of exposure to rabies, before any contact with the virus.**



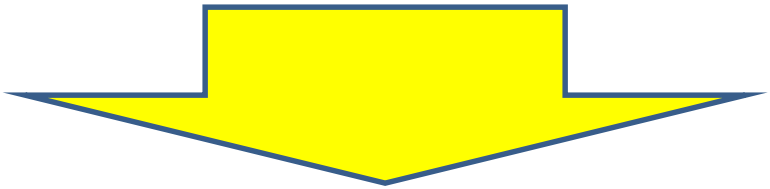
The PrEP protocol:

- Generally, 2 or 3 doses of an approved vaccine, administered intramuscularly (IM = upper deltoid) at a dose of 1 ml, according to the manufacturer's recommendations, on days 0, 7, and 21 or 28.
- Booster vaccination according to the risk group.

- PrEP should be offered to individuals with an increased risk of exposure to rabies: laboratory workers, veterinarians, forest rangers, zoo staff, spelunkers, etc.

Medical management following a bite (scratch or other contact) from an animal

- In the event of a bite, scratch by an animal, or contact with a rabid animal (example: contact of a wound with the saliva of an animal suspected of having rabies) it is imperative to act immediately as rabies is a fatal disease upon the appearance of the first symptoms =



1. Immediately report to local health authorities any animal bite on a human or any risk of contact with a rabid animal.
2. Immediate local care (First aid) = Crucial
3. Immediate medical care for the affected person (bitten or having come into contact with a rabid animal).
4. Management of the animal.

Immediate local care

- Washing and disinfection
- Primary closure decision (stitches).

- ***Washing and disinfection:***

  - Thoroughly and immediately clean the wounds of the exposed person with a large amount of water and soap to reduce viral load, preferably for 5 to 15 minutes.
  - Ethanol (70%), benzalkonium chloride (1 to 4%), povidone-iodine and iodine tincture are highly recommended rabic disinfectants.

➢ *Primary closure decision (stitches):*

- The decision to immediately close a dog bite wound depends on several factors, including the location of the wound, the time elapsed since the bite, and the quality of first aid.
- Immediate closure is generally preferred for facial bites and wounds treated within 8 to 12 hours following thorough cleaning and debridement.
- In contrast, it is often recommended to leave the wound open for puncture wounds, bites to the hands or feet, infected wounds, or those older than 24 hours.

Immediate medical care

- Immediate consultation to start post-exposure prophylaxis (PEP).
- It generally includes:
  - Rabies vaccination: A series of injections to be started as soon as possible (ideally within 24 hours).
  - Rabies serotherapy (Immunoglobulins): Administered directly into and around the wound for severe exposures (category III) to locally neutralize the virus.
  - Antibiotic therapy.
  - Verification of tetanus vaccination.

- According to the circumstances, public health authorities will immediately decide if a PPE is indicated.
- Individuals already vaccinated typically receive two doses of vaccine (on days 0 and 3).
- Unvaccinated individuals receive:
  - Essen schedule.
  - Zagreb schedule.
- Vaccination offers poor protection against genotypes 2, 3, 4, 5.

- **Essen schedule (5 doses): Injections on days J0, J3, J7, J14, and J28.**
- **Zagreb schedule (4 doses): Two doses on J0 (one in each arm/deltoid), then one dose on J7 and one on J21.**
- **Combined treatment: In case of severe injury = Category III),**
  - *Serotherapy (Immunoglobulins - IgAR): Administration of rabies immunoglobulins is necessary in addition to the vaccine starting from day one.*
  - *Vaccination (Essen or Zagreb).*

WHO guide for post-exposure prophylaxis based on the severity of the exposure

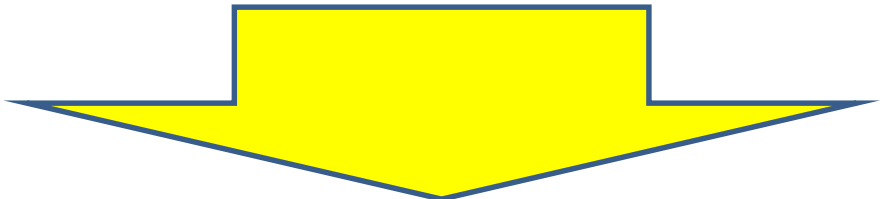
Catégorie d'exposition	Type d'exposition à un animal domestique ou sauvage, suspecté ou confirmé enragé ou non disponible pour le test	Prophylaxie post-exposition recommandée
I	Contact ou alimentation de l'animal Léchage sur peau intacte (pas d'exposition)	Aucune si une anamnèse peut être obtenue[a].
II	Peau découverte mordillée Griffures bénignes ou excoriations, sans saignement (exposition)	Administrer le vaccin immédiatement. Arrêter le traitement si l'animal est en bonne santé à l'issue de la période d'observation de 10 jours[b] ou si la recherche de la rage par les techniques de laboratoire appropriées est négative. Traiter comme une catégorie III en cas d'exposition aux chauves-souris.
III	Morsure(s)[c] ou griffure(s) ayant traversé la peau, léchage sur peau érodée ou contamination des muqueuses par la salive (léchage), exposition aux chauves-souris (exposition sévère)	Administrer le vaccin immédiatement, et les immunoglobulines rabiques, de préférence dès que possible après le début de la prophylaxie post-exposition. Les immunoglobulines rabiques peuvent être injectées jusqu'à 7 jours après l'administration de la première dose de vaccin. Arrêter le traitement si l'animal est en bonne santé à l'issue de la période d'observation de 10 jours[b] ou si la recherche de la rage par les techniques de laboratoire appropriées est négative.

Animal management

- **Declaration: Immediately report the animal to health authorities.**
- Domestic animal (dog and cat): If available: Placed under veterinary surveillance for 10 days OR 15 days.
- **Wild or dead animal:**
  - Never handle a carcass with bare hands.
  - Contact health authorities or veterinary services for brain analysis

❑ *Health surveillance (domestic dogs and cats)*

- Veterinary surveillance (France, Algeria, etc.) includes 3 certificates stating the absence of rabies signs:
  - Visit 1: within 24 hours of the bite.
  - Visit 2: on the 7th day after the bite.
  - Visit 3: on the 15th day after the bite.
- During this period, it is prohibited to vaccinate the animal against rabies, to separate from it, or to proceed with its euthanasia without a waiver.



- In case of signs of rabies, euthanize the animal and conduct a rabies screening test.
- According to WHO recommendations, the minimum observation duration for veterinary surveillance of dogs and cats is 10 days.
- Rabid dogs and cats will die during the 10-day quarantine (surveillance) period.

Recommendations post-exposure to rabies in humans in the United States

Note: There are various guidelines in other countries.

Potential source of infection: Dog, cat, or ferret

❖ ***Situation 1: Healthy animals belonging to an owner + All bites (any puncture of the skin by teeth)***

- Animal's outcome:

- Confinement; observation for at least 10 days, especially in cases of unprovoked attack (unprovoked aggression).

- Post-exposure prophylaxis in humans (PEP):

- No intervention or consideration in case of unprovoked attack.
- Yes, if signs of CNS involvement appear in the animal (during the period of .

Potential source of infection: Dog, cat or ferret

- The vaccination status of the animal should not be used to make a decision regarding the implementation (or outcome) of PEP.
- An unprovoked (spontaneous) attack by an animal is more likely to indicate rabies than a provoked attack.
- Bites from a healthy dog, cat, or ferret during feeding or handling should be considered provoked.

Potential source of infection: Dog, cat or ferret

❖ ***Situation 2: Healthy stray animals (available or escaped) + All bites (any puncture of the skin by teeth).***

- Fate of the animal:

If the animal is available = Euthanize immediately + submit the head for examination.

- Post-exposure prophylaxis in humans (PEP):

- Yes.
- Stop if laboratory results are negative, or continue if the animal is not available.

Potential source of infection: Dog, cat, or ferret

❖ ***Situation 3: Animals with signs of CNS + All bites (any puncture of the skin by teeth).***

- **Fate of the animal:**

Euthanize immediately + submit the head for examination.

- Post-exposure prophylaxis in humans (PEP):

- Yes.
- Stop if laboratory results (DFA) are negative.

Potential source of infection: Bat

❖ ***Situation 1: Bite, scratch, contact with mucous membranes (saliva/fluids) or high likelihood of direct contact (e.g., confined space).***

Note: Injuries caused by bats can be small and go unnoticed

- Fate of the animal:

Safely recover the bat + submit it for examination (if possible).

- Post-exposure prophylaxis in humans (PEP):

- Yes.
- Stop if laboratory results (DFA) are negative.

Potential source of infection: Wild carnivore

❖ ***Situation 1: Any bite (any puncture of the skin by teeth).***

- Animal disposition:

In case of capture, euthanize immediately + submit the head for examination.

- Post-exposure prophylaxis in humans:

- Yes, if laboratory results are positive or if the animal is at large.
- Stop if the test (DFA) is negative.

Potential source of infection: Small rodents*

❖ ***Situation 1: All bites (any perforation of the skin by teeth).***

- **Outcome for the animal:**

Generally not examined.

- Post-exposure prophylaxis in humans (PEP):

None, but consult public health authorities if the circumstances of the bite warrant PEP.

*Squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice. Lagomorphs are also affected. Larger rodents, such as groundhogs and beavers, have been infected in areas where raccoon rabies is endemic and should be tested.