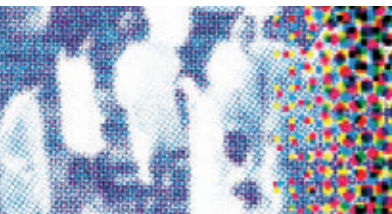
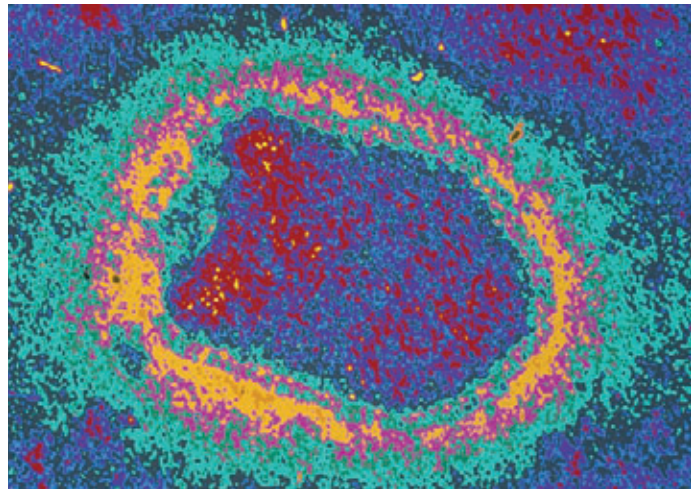


Pathologies

The Institut Pasteur
the Institut Pasteur
International Network
&
Rabies

*"Knowledge belongs
to all mankind"*
Louis Pasteur



Fighting infectious disease



The Institut Pasteur works to prevent and treat diseases, especially infectious ones, through research, training and public health activities.

Infectious diseases caused by pathogens (**viruses**, **bacteria**, **parasites** or **fungi**) kill 13 million people worldwide every year.

> Mobilizing researchers

The Institut Pasteur and the International Network focus their resources on research into infectious pathologies (HIV/AIDS, tuberculosis, malaria, etc.) and emerging diseases (SARS, influenza, dengue fever, hepatitis, West Nile fever, etc.).

> Spreading knowledge

To ensure that the results of the research benefit the people concerned, the Institut Pasteur works in close partnership with other research institutions and major public and private institutions at the national and international level. The aim is to contribute to improving human health through basic research, monitoring, and surveillance and by developing new diagnostic tools, medicines and vaccines.

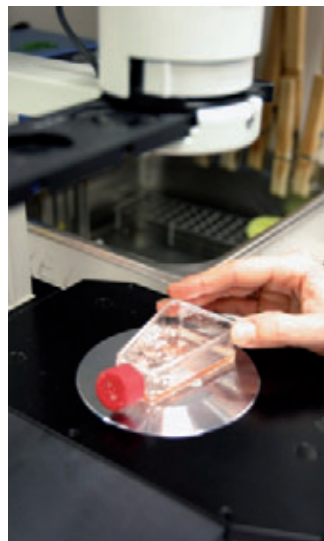
GLOSSARY

Virus : infectious agent invisible under an ordinary optical microscope. Viruses are distinguishable from bacteria because they have only one type of nucleic acid, RNA or DNA.

Bacterium: unicellular micro-organism without a nucleus, visible under a microscope, whose two main shapes are spherical (cocci) or elongated (bacilli).

Parasite : animal or plant organism which lives off its host.

Fungus: filamentous unicellular micro-organism that multiplies in a favourable environment and may cause disease (aspergillosis, mycoses, etc.).



Rabies

FACTS & FIGURES

- At least **55,000 people** die from rabies each year worldwide.
- **30 to 50% of deaths** occur in children **under 15 years of age**.
- **Over 90% of human rabies cases** are concentrated in **Asia and Africa**.
- Every year, approximately **14 million people** receive post-exposure prophylaxis after having been in contact with an animal suspected of carrying rabies.

Source: WHO

Transmission via wild animals

Numerous wild species around the world harbour variants of the rabies virus: mongooses in South Africa, jackals in the rest of Africa, polar foxes in Alaska and in Northern Canada, red foxes in Europe and North America, racoons in the United States, vampire bats in Latin America, etc.

Rabies is a fatal infection of the nervous system that kills at least 55,000 people worldwide each year, in spite of the existence of an effective vaccine since its development by Louis Pasteur in 1885.

> A lethal disease of animal origin

Rabies is virtually always lethal after the appearance of the first symptoms (anxiety, confusion). It is caused by a number of species belonging to the Lyssavirus genus, to which all mammals are vulnerable, and is conveyed from animals to humans mainly via exposure to infected saliva. Dogs, which are responsible for 90% of rabies cases, are the main vector for this disease, though it is also conveyed by wild animals (bats, wolves, foxes, etc.).

> Epidemiology

Animal rabies is widespread throughout the world and particularly in Africa and Asia. Children, who are more likely to play with stray dogs, are among the most exposed. In Europe and the Americas, bat rabies now constitutes the main risk for humans.

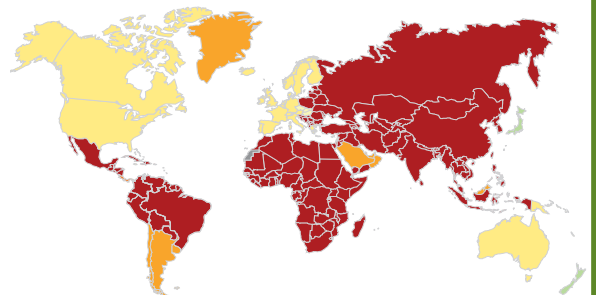
> Fighting on all fronts

A large percentage of the world population still has no access to the preventive vaccine or post-exposure prophylaxis. In addition, there is still no means of "curing" the disease once the symptoms have appeared. It is therefore essential to create awareness among the most vulnerable populations, improve tools for early diagnosis and identify antiviral molecules that are active against *Lyssaviruses*. Finally, the most effective strategy to prevent rabies in human is eradicating the virus in animals by means of vaccination.

Distribution of rabies risk worldwide

Source: WHO

- High risk
- Moderate risk
- Low risk
- No risk





Joseph Meister, the first person to benefit from post-exposure treatment for rabies, administered by Louis Pasteur.

Louis Pasteur and vaccination against rabies

In 1885, Louis Pasteur obtained his first success against rabies by vaccinating Joseph Meister, a 9-year-old boy presenting multiple deep bite wounds. In 1886, after more than 700 successful inoculations, Pasteur launched an international subscription with a view to opening an institute dedicated to rabies treatment and the study of Pasteurian science. In 1887, the Institut Pasteur was born.

FOR INFORMATION

Since 2007, **World Rabies Day** takes place every **September 28th**. It aims to spread awareness in local populations and inform them about:

- the effects of the disease in humans and animals
- existing preventive measures
- the means of eradicating human rabies by focusing on the control of animal reservoirs.

www.rabiescontrol.net

The disease

Rabies is a zoonosis, a disease that is transmitted from animals to humans. Each species is infected by a specific virus type.

> Transmission

Rabies is not contagious between humans except as a result of a graft or organ transplant. The rabies virus becomes present in animals' saliva as the disease advances and is transmitted by biting, scratching or licking of the skin or mucosa. There are three categories of contact according to the associated degree of risk: having touched or fed suspect animals with no resulting skin damage; having been scratched slightly but without bleeding, or having been licked on scratched skin; and having been bitten or been in very close contact with bats.

> Symptoms and clinical progression

The rabies virus is neurotropic: it modifies nervous system function. It does not cause anatomically visible brain lesions but disturbs the function of neurons, in particular those responsible for cardiac activity and respiration.

The incubation phase is highly variable and may last from a few days to several months. This is followed by the symptomatic phase, which usually begins with difficulty swallowing and neuropsychiatric disturbances (anxiety and agitation). Irrational fear of water, known as hydrophobia, sometimes occurs toward the end of the disease. The disease progresses to a coma and death within a few days, often via respiratory arrest.

> Vaccination and treatment

There are safe and effective vaccines available to prevent rabies both in humans and animals. They can be used before and after any presumed exposure.

Preventive vaccination is recommended for all individuals who live in or travel to endemic zones, or people exposed to rabies in a professional context.

Post-exposure prophylaxis should start with meticulous cleansing of the wound or point of contact with soap and water. Vaccination (4 to 5 injections over a period of a month) should be carried out as soon as possible, ideally in the first few hours after exposure and always before the appearance of initial symptoms. This should be combined with serum treatment in case of serious contact or in people with weakened immune systems.



Tridimensional structure of a *Lyssavirus* matrix protein.



Research

The Institut Pasteur has played a leading role in the prevention and control of rabies worldwide ever since the rabies vaccine was developed by its founder in the late 19th century.

> Epidemiological and genetic studies

Several groups in Paris and in the Institut Pasteur International Network are involved in research programmes on the epidemiology of human and animal rabies. At the Institut Pasteur, the Provisional Unit on *Lyssavirus* Dynamics and Host Adaptation, which is also a National Reference Centre for rabies and a World Health Organisation Collaborating Centre (WHOCC), has published the first genomic and evolutionary analysis of all known *Lyssavirus* genotypes. The phylogeography of the canine virus is being studied in a collaborative effort between researchers in Paris, Dakar, Bangui and Côte d’Ivoire. Also, at the Institut Pasteur in Iran, researchers demonstrated that wolves play a crucial role in the transmission of the disease in their country.

Finally, researchers at the Institut Pasteur in Cambodia have estimated the number of human cases in the country, highlighting the impact of this “neglected” pathology.

GLOSSARY

Hydrophobia:

patients in the terminal phase of rabies may experience an irrational fear of liquid and contact with it can cause an intolerable sensation of burning

Phylogeography:

the study of the principles and processes that govern the geographic distribution of genealogical lineages, including those of viruses

DNA chip:

an array of DNA molecules attached to a small surface (glass, silica or plastic) in order to analyse gene expression in cells, tissues, organs, etc.

Serum:

a liquid obtained by removing cells and coagulation proteins from blood, containing antibodies in solution. When injected, purified serum from a horse vaccinated against rabies can ensure immediate protection following an infectious bite

RABMEDCONTROL: controlling rabies in North Africa

This project, financed by the European Union, involves the participation of the Institut Pasteur in Paris and numerous institutes from nine countries around the Mediterranean basin, including the Instituts Pasteur in Tunisia, Morocco and Algeria.

Its goal is to collect epidemiological and virological data on the human and animal forms in North Africa in order to improve management of the disease.

Such multidisciplinary studies will help improve our understanding of the distribution of dog and bat populations and of the behaviour of human populations, both of which can influence the dynamics of rabies.

→ www.rabmedcontrol.org



> Improving diagnostic techniques

Clinical management of rabies is mainly based on diagnosis, so that action can be taken before the first symptoms appear. In Paris, the Provisional Unit on *Lyssavirus* Dynamics and Host Adaptation has collaborated with researchers from the Instituts Pasteur in Madagascar, Dakar and Cambodia to validate a method of early biological diagnosis using saliva samples and skin biopsies.

In addition, the development and use of DNA chips have proved useful in looking for new rhabdoviruses and diagnosing infections of the central nervous system, including rabies.



Dogs are the principal vector for rabies.

> Vaccines and treatments

A new protocol for intradermal administration of the human vaccine, cheaper than and equally as efficient as the current protocol, has been approved at the National Reference Centre and WHOCC for rabies in Paris. The Instituts Pasteur in Tunis and Algeria, together with the three Vietnamese institutes in the Network, are also working to develop new vaccines and anti-rabies sera for human use.

In Tunis, a research group is also testing a veterinary vaccine that conveys long-lasting immunity against the canine virus. It has developed a culture technique that uses no human or animal components.

The Provisional Unit on *Lyssavirus* Dynamics and Host Adaptation at the Institut Pasteur is participating in one of the largest European research programmes in structural genomics (www.vizier-europe.org), which aims to understand the interactions between molecules involved in viral proliferation in the body by studying their three-dimensional structure.

Another Paris group, the Provisional Unit on Antiviral Strategies, is looking for molecules that are active against the rabies virus and is studying replication phenomena so as to identify therapeutic targets.

> Immunological research

The Viral Neuro-Immunology Unit is studying neuronal dysfunction following infection and the resulting immunological consequences.

Another approach consists in testing the inhibitory potential of molecules targeting viral replication. This method has allowed for the identification of a natural immunoinhibitor that exacerbates rabies encephalitis in mice. The idea is now to find a way of neutralising this inhibitor.

> Knowledge transfer

The institutes in the International Network regularly organise courses, workshops and seminars on rabies: prophylaxis of human rabies in Cambodia; organisation of antirabies centres, updates on post-exposure prophylaxis and preventive vaccination, and training in vaccine pharmacovigilance in Madagascar; laboratory diagnosis in Ho Chi Minh City, etc.

In addition, a course on rabies has been co-organised in Shanghai with WHO, the Chinese CDC and the Institut Pasteur in Shanghai – Chinese Academy of Sciences.

Rabies surveillance in France

The National Reference Centre for rabies at the Institut Pasteur performs epidemiological surveillance for rabies in France.

It coordinates 66 rabies treatment centres and 21 sub-centres, in which 8,600 consultations took place in 2008, resulting in 4,500 post-exposure treatments.

FOR INFORMATION

- In 2008, the institutes of the Institut Pasteur International Network administered **500,000 doses** of rabies vaccine on five continents.
- **The AfroREB network** brings together rabies experts from the Instituts Pasteur in Sub-Saharan Africa and North Africa to share information and improve programmes to better control the disease.
www.afroreb.info

At the National Reference Centre for rabies in Paris,

researchers have been observing the evolution of rabies incidence in bat colonies in Europe over the past 12 years.

There is a potential risk that *Lyssaviruses* harboured by bats may be transferred to humans, which justifies the prohibition on entering certain caves. This animal has already been the source of four human cases on the continent since 1985. More infectious viral variants could emerge.

Perspectives

> Improving diagnosis and treatment

Researchers from the Provisional Unit on *Lyssavirus* Dynamics and Host Adaptation at the Institut Pasteur are exploring an innovative therapeutic approach based on blocking the action of a *Lyssavirus* matrix protein.

For the time being, given the absence of a therapeutic solution once the virus has reached the nervous system, prevention of human rabies is largely based on early diagnosis and improving access to post-exposure prophylaxis. Recent research shows that it is possible to develop less costly vaccines without diminishing their efficacy.

> From one *Lyssavirus* to the next

Populations from developed and developing countries may both be exposed to many variants of the rabies virus. It is important to develop biological products (vaccines and anti-rabies immunoglobulins) with a larger spectrum of activity, particularly in view of the viral variants that circulate within bat colonies.

> Controlling neuro-degenerative diseases

Rabies viruses can only propagate between live neurons. Starting from this observation, researchers in the Viral Neuro-Immunology Unit at the Institut Pasteur are trying to get a better understanding of the interactions between virus and neurons. Their work could also apply to neurons affected by degenerative phenomena.

> Eradicating canine rabies

The problem of rabies cannot be resolved without better control of the canine reservoir, which is the primary source of human disease in the world. In Paris, researchers are therefore working on the development of a veterinary parenteral vaccine with a wider spectrum.

Other work bears on the development of an oral vaccine designed for wandering dogs in endemic zones. In France, in the 1990s, fox rabies was eliminated in just a few years using a similar technique.

The units working on rabies at the Institut Pasteur

- Provisional Unit on *Lyssavirus* Dynamics and Host Adaptation
- Provisional Unit on Antiviral Strategies
- Viral Neuro-Immunology Unit



Cambodian child bitten by a potentially rabid dog.

FOR INFORMATION

- WHO estimates that post-exposure prophylaxis helps avoid approximately **300,000 deaths a year** in Asia and Africa.
- The average cost of rabies vaccination is somewhere **between 40 and 49 dollars in Africa and Asia**, whereas the average salary is one to two dollars per person per day in most endemic countries.

International Network institutes working on rabies

- Institut Pasteur in Algeria
- Institut Pasteur in Bangui (WHOCC), CAR
- Institut Pasteur in Cambodia
- Institut Pasteur in Côte d'Ivoire
- Institut Pasteur in Dakar, Senegal
- Institut Pasteur in Ho Chi Minh City, Vietnam
- Institut Pasteur in Iran (WHOCC)
- Institut Pasteur in Madagascar
- Institut Pasteur in Morocco
- Institut Pasteur in Nha Trang, Vietnam
- Institut Pasteur in Tunis, Tunisia
- NIHE (Hanoi, Vietnam)

Institut Pasteur: a worldwide presence

The Institut Pasteur and the International Network work in close collaboration with the WHO.



A not-for-profit private foundation, the Institut Pasteur performs research, education and public health activities in the public interest since its creation in 1887.

At the nexus of several disciplines, including microbiology, immunology, and molecular biology, it is recognized worldwide for its contributions to biomedical science.

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The Institut Pasteur is at the core of an International Network of some thirty institutes on all five continents, most of which are independent entities governed by their national authorities.

The institutes of the International Network are associated in partnerships and cooperation agreements covering scientific research, training and public health services, and they share common values and objectives.

