RABIES

Aetiology Epidemiology Diagnosis Prevention and Control References

AETIOLOGY

Classification of the causative agent

Rabies is caused by neurotropic RNA viruses of the genus *Lyssavirus* in the family *Rhabdoviridae* of the order Mononegavirales, and is transmissible to all mammals.

Twelve distinct lyssavirus species can be distinguished within the genus, namely classical rabies virus (RABV), Lagos bat virus (LBV), Mokola virus (MOKV), Duvenhage virus (DUVV), European bat lyssaviruses type-1 (EBLV-1) and type-2 (EBLV-2), Australian bat lyssavirus (ABLV), Aravan virus (ARAV), Khujand virus (KHUV), Irkut virus (IRKV), West Caucasian bat virus (WCBV), Shimoni bat virus (SHIBV). In addition, two other newly identified lyssavirus have been proposed to the International Committee on the Taxonomy of Viruses (ICTV) as tentative new species.

Of all the lyssaviruses known to date, RABV is the most important one for public and animal health.

Resistance to physical and chemical action

Temperature:	Does not survive for more than 24 hours in dead animals when temperatures reach 21°C (70°F), but is highly resistant for extended periods at low or freezing temperatures
pH:	Sensitive to very low pH (below 3) or very high pH (greater than 11)
Chemicals/ Disinfectants:	Inactivated by sodium hypochlorite, 45–75% ethanol, iodine preparations, quaternary ammonium compounds, formaldehyde, phenol, ether, trypsin, β-propiolactone, and some other detergents
Survival:	Does not survive well outside its host (in dried blood and secretions) as it is susceptible to sunlight and desiccation. It is also susceptible to ultraviolet radiation

EPIDEMIOLOGY

- Rabies is a zoonotic disease that can affect all mammals.
- Carnivores circulate different rabies virus (RABV) variants and act as a reservoir for rabies, with occasional transmission to humans.
- Classical rabies virus is found throughout the world.
- Rabies infection is maintained in two epidemiological cycles, one urban and one sylvatic. In the urban rabies cycle, dogs are the main reservoir host. This cycle predominates in areas of Africa, Asia, and Central and South America. The sylvatic (or wildlife) cycle is the predominant cycle in the northern hemisphere. It can also present simultaneously with the urban cycle in some parts of the world.
- Despite being 100% preventable, canine-mediated rabies is one of the most important zoonosis and is estimated to cause up to 70,000 human deaths per year mostly affecting people in rural areas.
- It has important social costs due to human mortality and high economic consequences due to the losses in livestock and the cost of the implementation of preventive and control measures in both animals and humans.

Hosts

- A broad spectrum of animals can be infected experimentally with rabies virus.
- All mammals are susceptible to varying degrees, particularly members of the order Carnivora and Chiroptera.

Transmission

- Rabies virus can be transmitted between mammals, whether they belong to the same or different species.
- Rabies virus is primarily transmitted through the saliva of an infected animal. Saliva becomes infectious a few days prior to the onset of clinical signs.
- Infection occurs primarily via bite wounds, or infected saliva entering an open cut or wound or mucous membrane, such as those in the mouth, nasal cavity or eyes.
- Occasional, albeit rare, transmission by inhalation of infected aerosol has been described.

Sources of virus

- The main source of virus is the saliva and brain tissue.

Occurrence

- Rabies virus is spread worldwide in domestic and wild animals, as well as bats in the Americas, and is responsible for the overwhelming majority of reported animal and human rabies cases. Other lyssaviruses appear to have a more restricted geographical and host range, with the majority having been isolated from bats.
- The disease remains endemic in some countries with rabies being present in domestic and/or wild animals.
- Some countries have implemented control measures and succeeded in being free from the disease according to the OIE requirements.

For more recent, detailed information on the occurrence of this disease worldwide, see the OIE World Animal Health Information Database (WAHID) interface [http://www.oie.int/wahis/public.php?page=home] or refer to the latest issues of the World Animal Health and the OIE *Bulletin*.

DIAGNOSIS

The incubation period varies from a few days to more than 7 years. For the purposes of the OIE *Terrestrial Code* the incubation period is considered to be 6 months.

Clinical observations may only lead to a suspicion of rabies because signs of the disease are not pathognomonic and may vary greatly from one animal to another. The only way to undertake a reliable diagnosis is to identify the virus or viral antigen/viral RNA using laboratory tests.

Clinical diagnosis

- All lyssaviruses cause clinical disease indistinguishable from classical rabies.
- Clinical signs in animals will vary depending on the effect of the virus on the brain. Typical signs include sudden behavioural changes that can lead to increased aggression and progressive paralysis leading to death.
- Clinical rabies could be presented in two different forms: *furious rabies* when animals show aggressive behaviour, and *dumb or paralytic rabies* that refers to infected animals in which the behavioural changes are minimal, and the disease is manifest principally by paralysis.

Lesions

- No gross post-mortem lesions can be considered pathognomonic in domestic or wild animals.
- The typical histological signs, found in the central nervous system, are multifocal, mild, polioencephalo-myelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells and glial nodules. Negri bodies can be seen in some but not all cases.

Differential diagnosis

Any suspected mammalian encephalitis and neurological disorder must be considered in the differential diagnosis.

Laboratory diagnosis

Laboratories working with lyssaviruses or suspect material must comply with national biocontainment and biosafety regulations and they should also comply with the guidelines for Risk Group 3, as described in Chapter 1.1.3 *Biosafety and biosecurity in the veterinary diagnostic microbiology laboratory and animal facilities* of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*).

Samples

- Laboratory techniques are preferably applied on samples from the central nervous system of the suspected animal.
- Samples should be collected following the opening of the skull.
- If the skull cannot be opened there are two alternative routes for collected brain samples: the occipital foramen route and retro-orbital route.
- Shipment conditions must be considered to be part of the 'rabies diagnostic chain' and should follow the description given in the OIE *Terrestrial Manual*.

Procedures

Laboratory demonstration of rabies viral antigen, nucleic acid or viable virus will be necessary for a positive diagnosis.

Immunochemical identification of rabies virus antigen:

- Fluorescent antibody test (FAT) – Gold standard
- Immunochemical tests
- Enzyme-linked immunosorbent assay (ELISA)
- Rapid immunodiagnostic test (RIDT)

Detection of rabies virus after inoculation:

- Cell culture test (also referred to as rabies tissue culture infection test – RTCIT)
- Mouse inoculation test
  (NB: wherever possible, virus isolation on cell culture should be considered in preference to the mouse inoculation test)

Molecular techniques

Molecular methods, such as the reverse transcription polymerase chain reaction (RT-PCR) and other amplification techniques, are playing an increasingly important role in many countries but are not recommended currently for routine post-mortem diagnosis of rabies if brain tissue is available, when the FAT should be used.

Typing of the virus can provide useful epidemiological information and should be undertaken in specialised laboratories such as OIE or WHO Reference Laboratories

Suspect cases of rabies, especially those in recognised rabies-free countries, should be required to undergo an OIE recognised confirmatory diagnostic test (virus isolation or intracerebral mouse inoculation) on any sample that initially tests positive using an OIE gold-standard diagnostic test (FAT) that detects rabies virus antigen in brain samples.

Serological testing is rarely useful for ante-mortem diagnosis because of late or failing seroconversion and the high mortality rate of host species, but is very useful for assessing seroconversion following vaccination and for epidemiological studies.

For more detailed information regarding laboratory diagnostic methodologies, please refer to Chapter 2.1.13 *Rabies* in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading "B. Diagnostic Techniques"

PREVENTION AND CONTROL

From a global public health perspective, the dog should be considered a main target for rabies elimination as this principal reservoir is responsible for the overwhelming majority of reported animal and human rabies cases. It has been demonstrated that the disease can be successfully controlled in certain wild carnivores, such as red foxes, raccoon dogs and coyotes. Apart from dogs, other companion animals (such as cats and ferrets) and livestock pose a risk for human exposure and would benefit from inclusion in any national vaccination programme. Additionally, vaccination of livestock in rabies endemic areas is recommended as it secures livelihoods in many parts of the world.

In countries where the disease is endemic, measures are implemented to address and reduce the risk of infection in susceptible populations (wildlife, stray and domestic animals) in order to create a buffer between the animal disease reservoir and humans.

A rabies control programme should consider:

- **Socio-cultural framework,** including public awareness, the promotion of responsible pet ownership and animal welfare.
- **Technical framework,** including vaccination programmes for both domestic and wildlife animals, improving laboratory confirmed disease surveillance and reporting, appropriate diagnostic capability, dog population management and animal movement control.

Sanitary prophylaxis

- Rabies should be notifiable in the whole country and any change in the epidemiological situation or relevant events should be reported.
- An effective system of disease surveillance should be in operation including an on-going early detection programme to ensure investigation and reporting of suspected cases of rabies in animals.
- Specific regulatory measures for the prevention and control should be implemented consistent with the recommendations in the *Terrestrial Code*, including vaccination, animal identification and effective national and international control movements of dogs, cats and ferrets.

Medical prophylaxis

Rabies vaccines produced in compliance with OIE requirements protect against all variants of rabies virus except against the MOKV and LBV variants that generate little or no cross-protection.

Rabies vaccines are defined as a standardised formulation containing defined amounts of immunogens. These immunogens are either inactivated (killed), live-attenuated or biotechnology-derived.

Before newly developed vaccines can be licensed, the duration of immunity resulting from their use should be determined in vaccinated animals of the target species. Vaccines should confer protective immunity for at least 1 year.

Rabies vaccine for injectable use

- Live-attenuated vaccines have been widely used for injection in domestic animals. However, several of these products have been documented to cause rabies in vaccinated animals, and injectable use should be discontinued.
- The rabies virus glycoprotein biotechnology-derived vector vaccines are not live rabies virus vaccines. They are prepared by inserting non-infectious rabies virus nucleic acid coding for rabies virus glycoprotein into a vector such as avipox for injectable vaccine. As these do not contain live rabies virus, animals vaccinated with rabies virus glycoprotein vaccines should not be restricted from entry into countries that have restrictions on entry of animals vaccinated with live rabies virus vaccines.

Rabies vaccine for oral use

- Vaccines for oral use are indicated for feral and wild animals that cannot be reached physically.
- All vaccines currently used for oral vaccination programmes are either modified live vaccines or biotechnology-derived vaccines
- Safety and efficacy in target animals and safety in non-target species must be demonstrated. Oral vaccination will request periodical monitoring of the impact of vaccination programme.

For more detailed information regarding vaccines, please refer to Chapter 2.1.13 *Rabies* in the latest edition of the *OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animal*s under the heading "C. Requirements for Vaccines".

For more detailed information regarding safe international trade in terrestrial animals and their products, please refer to the latest edition of the OIE *Terrestrial Animal Health Code*.

REFERENCES AND OTHER INFORMATION

- Compendium of Animal Rabies Prevention and Control (2011) http://www.cdc.gov/mmwr/pdf/rr/rr6006.pdf
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- Rabies and Rabies-Related Lyssavirus (2012) – The Center for food security and Public Health http://www.cfsph.iastate.edu/DiseaseInfo/index.php?lang=en
- World Organisation for Animal Health (2013). – Terrestrial Animal Health Code. OIE, Paris.
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- The Blueprint for Rabies Prevention and Control. http://www.rabiesblueprint.com/
- World Health Organisation. 2013 Expert Consultation on Rabies, Second report. World Health Organ. Tech. Rep. Ser. 982, 1-150

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The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Scientific and Technical Department (scientific.dept@oie.int). Last updated 7 May 2014.