18 Rabies

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics of the vaccines. When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

Key changes

This chapter has been updated as follows:

- changes in definition of types of exposure
- clarification of the groups who should receive rabies pre-exposure immunisation

Contents

18.1 Introduction

Rabies is an acute viral encephalomyelitis caused by a lyssavirus. Infection usually results from the bite or scratch of a rabid animal. Dogs are responsible for up to 99% of human rabies cases.

The virus attacks the central nervous system, causing progressive paralysis, encephalitis and coma. Once symptoms are present, rabies is invariably fatal.

Rabies is usually caused by rabies virus genotype 1 (classical rabies), less commonly by rabies-related lyssaviruses. European bat lyssavirus (EBLV1 and 2) infects insectivorous bats in Europe. Since 1977, four human cases of EBLV infection have been reported across Europe.

18.2 Epidemiology

Any warm-blooded animal may be infected with rabies virus, including dogs, cats, foxes, bats, skunks, racoons and monkeys. Worldwide 40-70,000 cases of human rabies occur annually, over 90% from dog bites in low-resource countries. In these countries, 60% of animal bites occur in or around the home, increasing the risks for those visiting friends and relatives (VFRs). Almost 50% of deaths occur in children, who are more vulnerable than adults to attack by animals.

No indigenous rabies cases have been reported in Ireland since 1923. Very few cases of rabies in humans are reported in the EU.

Some countries (e.g. the UK, Australia) that are declared rabies-free have rabies-related lyssaviruses in their bat populations.

Any bite, lick or scratch from a warm-blooded animal in an endemic area must be considered as high risk and specialist advice should be sought as soon as possible.

Transmission

Infection is usually transmitted by the bite or scratch of a rabid animal. The virus may also be passed when infected saliva comes in contact with broken skin, mucous membranes or the cornea. Laboratory workers in contact with specimens containing the virus are at risk of occupational contact. Aerosol transmission is possible and may be important in rabies-infected bat caverns. Human-to-human transmission is extremely rare, the only documented cases involved corneal and solid organ transplantation from infected patients who died prior to diagnosis.

Types of contact are:

Category I – touching or feeding animals, licks on intact skin.

Category II - nibbling of uncovered skin, minor scratches or abrasions without bleeding.

Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from licks, exposure due to direct contact with bats.

18.3 Effects of Rabies

The incubation period of rabies is generally between 2 and 12 weeks but may range from 4 days to many years. In over 90% of cases the disease presents within 1 year. Factors that tend to shorten the incubation period include younger age, inoculation near well-innervated parts of the body, inoculation near the head and neck, and more extensive wounds.

Untreated rabies is almost invariably fatal; the rare cases of survival after symptoms have developed had some pre- or post-exposure treatment.

Initial viral replication takes place in the tissues at the point of entry, persisting for between 48 and 72 hours. The virus moves along the axonal sheaths in peripheral nerves towards the central nervous system. Viral spread then occurs to the peripheral nerves; there is no antibody response until the onset of clinical symptoms.

Symptoms are variable. Early symptoms are non-specific and include pain and paraesthesia at the inoculation site. Low-grade fever, malaise, anorexia, headache, nausea and vomiting are common. The patient may be excitable or irritable, with more classical hypoglossal spasm associated with water contact (hydrophobia) or blowing in the face (aerophobia). Rising intracranial pressure leads to decreased level of consciousness and convulsions. Central and peripheral nerve impairment leads to progressive respiratory distress. A wide variety of cardiac dysrhythmias can occur. Other causes of acute encephalitis, Guillain-Barré syndrome, tetanus, poliomyelitis, and neurological adverse reactions to drugs and poisons are among the differential diagnoses.

18.4 Rabies vaccines

Vaccines available in Ireland are either Human Diploid Cell vaccines (HDCV) or inactivated, produced on purified chick embryo cells.

Licensed vaccines

- Rabies vaccine BP (1ml/dose).
- Rabipur (1ml/dose)
- Verorab (0.5ml/dose).

Not all are currently marketed.

They can be used interchangeably.

They are available through the National Cold Chain Service or from Cherry Orchard Hospital (Tel. 076 695 5000) or directly from the manufacturer.

An up to date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

Rabies vaccines should be stored at +2°C to +8°C. After reconstitution with sterile diluent, the vaccines must be used within 6–8 hours. The shelf-life of these vaccines is at least 3 years, provided they are stored at +2°C to +8°C and protected from sunlight.

The vaccines should not be used after the expiration date given on the package and container.

Licensed indications: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) against rabies in all age groups

Dose, route and schedule
The dose is ≥2.5IU, the entire contents of the vial.

The preferred route is IM in the deltoid, or anterolateral thigh for those aged 0-12 months. Either route can be used in those aged 12-36 months. Although approved by the WHO, NIAC does not recommend the intradermal (ID) route for routine use. It may be used by suitably qualified and experienced vaccinators for PrEP only. PEP should always be administered intramuscularly.

PrEP and PEP regimens require a series of vaccine injections.

Pre-exposure Prophylaxis (PrEP):
In previously unvaccinated individuals, three doses should be administered according to the conventional or rapid regimen shown in Table 18.1.

Table 18.1 Pre-exposure Prophylaxis

	Conventional Regimen	*Rapid Regimen**
Dose 1	Day 0	Day 0
Dose 2	Day 7	Day 3
Dose 3	Day 21 (or 28)	Day 7 *Booster required 12 months later*

*The rapid regimen should only be considered for those aged 18-65 years not able to complete the conventional pre-exposure prophylaxis regimen within 21 or 28 days before protection is required.

Post-exposure Prophylaxis (PEP)
The indication and procedure for PEP depend on the type of contact with the suspected rabid animal and immunisation status of the patient.

Category I: no PEP is required

Category II: immediate vaccination

Category III: immediate vaccination, and administration of HRIG if indicated.

Schedule
One of the following four-dose regimens may be used:

i. IM, one site on days 0, 3, 7 and 14-28, **or**

ii. IM, two sites on day 0 and one site on days 7 and 21.

Vaccine should always be administered when a category III exposure is recognised, even months or years after the contact. However, the likelihood of developing clinical rabies declines progressively during the 12 months after the exposure, with clinical rabies occurring only rarely after 12 months.

For categories II and III, thorough washing and flushing with soap or detergent and copious amounts of water of all bite wounds and scratches should be done as soon as possible.

Rabies vaccines should never be withheld, regardless of whether or not HRIG is available.

All travellers to areas of risk should be advised to seek immediate medical aid if an animal bite or scratch is sustained, and should be given advice on wound toilet

Recommendations

Pre-exposure prophylaxis (PrEP) for those at high risk

Those who are at continuous or frequent risk of exposure should be offered pre-exposure vaccine. Groups in these risk categories include:

- Laboratory workers handling or potentially handling the virus
- Those likely to be in direct contact with rabies-prone animals. This includes:
  - Staff at animal quarantine centres
  - Staff at zoos
  - Staff at research and acclimatisation centres where rabies-prone animals are housed
  - 'At-risk' staff at ports and airports, e.g. Department of Agriculture and Food Inspection staff
  - Dog wardens
  - Animal workers who regularly travel to rabies enzootic areas
  - Authorised carrying agents for imported Rabies-prone animals
  - Selected National Parks and Wildlife staff who may handle bats, based on risk assessment
  - Workers in enzootic areas at special risk (e.g. veterinary staff, zoologists)
- Health-care workers who have or may come into close contact with a patient (or their clinical specimens) with probable or confirmed rabies
- Adults and children living or travelling to rabies-endemic areas (particularly children, who may be more at risk or who may not report an exposure)

Immunocompromised persons may have a sub-optimal immune response to the vaccine.

Post vaccination serological testing

Post vaccination serology is recommended for

i. those at continuous or frequent risk, to determine the need for a booster dose.

ii. those who had a severe reaction to a previous dose of rabies vaccine, to determine if a course should be completed.

Most travellers are at infrequent risk and do not require serological testing.

When indicated, antibody assay should be performed 2 – 4 weeks after the last dose. An additional dose should be considered if the antibody titre is less than 0.5 IU/ml.

Booster doses

Booster doses are recommended for:

a. A booster is required one year after an accelerated course of PrEP (0,3,7 regime).

b. Those at regular and continuous risk.

- A booster dose is recommended one year after the primary course, and then 3 to 5 yearly
- Antibody titres are advised 6 monthly for those who work with live rabies virus; they may be given booster doses if the titre is below 0.5IU/ml.

c. Those with frequent episodic exposure, e.g. rabies diagnostic workers, veterinary surgeons and staff, and wildlife rangers conducting bat research.

Antibody titres should be checked every 3 years and boosters administered if the titre is below 0.5IU/ml.

Those at increased but infrequent risk of episodic exposure who are fully vaccinated do not require further booster doses.

Boosters should not be administered more frequently than every 3 years to minimise the possibility of localised reactions to the vaccine.

Contraindications

Anaphylaxis to any of the vaccine constituents

However, as rabies infection is generally fatal, there are no contraindications to post-exposure vaccination. Consider using an alternative Rabies vaccine. Facilities should be in place to monitor the vaccinated person and recognise and treat severe allergic reactions.

Precautions

Acute severe febrile illness – defer until recovery, unless used for post-exposure management.

Pregnancy. Pre-exposure vaccine may be given to pregnant women if the risk of exposure to rabies is high and rapid access to post exposure prophylaxis will be limited. Post exposure treatment should be given when indicated. Rabies vaccines and rabies immunoglobulin are considered safe to use in pregnant and lactating women, HIV-infected and other potentially immunocompromised individuals.

Adverse reactions
Very common: injection site erythema, pain and/or swelling, particularly following ID administration in case of repeat vaccination.

Common or very common general reactions: dizziness, fever, gastrointestinal symptoms, headache, myalgia, urticarial rash.

Pregnancy and breastfeeding
Rabies vaccines are safe and effective in pregnant and lactating women.

Post-exposure prophylaxis
Treatment must be started as soon as possible after exposure.
Moreover, treatment should be considered, *irrespective of the period between exposure and presentation*, unless the individual is fully vaccinated and rabies antibodies can be detected. Anyone with a possible exposure to rabies virus should seek immediate medical attention.

Treatment depends upon the circumstances of the exposure.

Specialist advice from Cherry Orchard Hospital (076-6955000) or HPSC should be sought for risk assessment and when post-exposure immunisation +/- immunoglobulin may be indicated.

1. As soon as possible
- The wound should be washed thoroughly with soap or detergent and water and rinsed completely. It is important not to mix disinfectant with soap during washing, as detergents can negate the effects of disinfectant.
- The wound or site of exposure (e.g. mucous membrane) should be held under a running tap for at least 10 minutes.
- For Category III wounds in those not fully vaccinated, HRIG should be infiltrated into the depth of the wound and around the wound (see section 18.3).
- Primary suturing should be avoided or postponed, as it may increase the risk of introduction of rabies virus into nerves.
- Tetanus prophylaxis and measures to control bacterial infection should be administered as indicated.

2. Risk assessment

Risk assessment of each case of possible exposure should include the following:

- *Country of exposure (or the country of origin of the animal):* Up-to- date information on rabies by country can be found at http://www.who-rabies-bulletin.org/ or http://www.cdc.gov/rabies or by contacting the National rabies advisory centre at Cherry Orchard Hospital (Tel. 076 695 5000).
- *Type, severity and site of the wound*: Highest risk wounds are those with broken skin, or where mucus membranes are contaminated with the animal's saliva or body fluids. Proximal bites, such as the face represent a greater risk than distal wounds.
- *Circumstances of bite:* Unprovoked bites carry a much higher risk than provoked bites.
- *Animal involved:* Bat rabies may be suspected if the bat is sick, grounded without injury or if an uninjured bat is found dead. If the bat is available, urgent testing is required.
- *Vaccination status of the animal (if known):* Regularly vaccinated animals are much less likely to be infected with rabies.
- *Immune status of the individual involved:* Fatal rabies encephalomyelitis is extremely unlikely in a fully immunised individual and is virtually certain to be prevented by an appropriate course of PEP, if given sufficiently early.

3. Post exposure prophylaxis (PEP)

Specialist advice from Cherry Orchard Hospital or the HPSC should be sought when post-exposure immunisation and immunoglobulin seem indicated. Management depends on the type of contact with the rabid animal.

Types of contact are:

Category I – touching or feeding animals, licks on intact skin.

Category II - nibbling of uncovered skin, minor scratches or abrasions without bleeding.

Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from licks, exposure due to direct contact with bats.

All category II and III exposures assessed as carrying a risk of developing rabies require PEP. The risk is increased if:

- the biting mammal is a known rabies reservoir or vector species
- the exposure occurs in a geographical area where rabies is still endemic
- the animal looks sick or displays abnormal behaviour
- a wound or mucous membrane was contaminated by the animal's saliva
- the bite was unprovoked
- the animal has not been vaccinated.

All immunosuppressed subjects should be given Human Rabies immunoglobulin (HRIG) following Category ll or lll exposure.

In the event of a Category ll or lll exposure, persons who have previously been immunised should receive 2 further doses of rabies vaccine on days 0 and 3.

18.5 Human Rabies Immunoglobulin (HRIG)

The mainstay of post exposure prophylaxis is rabies vaccine. HRIG may provide short term immunity in the first 7 days after the commencement of active immunisation. After 7 days the antibody level induced by active immunisation (vaccine) is many orders of magnitude greater that can be provided by passive immunisation with HRIG.

After thorough wound cleansing, HRIG should be infiltrated into the depth of the wound and around the wound as much as anatomically feasible. Any remainder should be injected at an intramuscular site distant from that of the vaccine, e.g. anterolateral thigh or deltoid.

Human Rabies immunoglobulin (HRIG)
Recommendations
Management of category III exposures of those not fully vaccinated against rabies.

HRIG should be administered only once, at or as soon as possible after the initiation of PEP.

Suturing of wounds should be delayed after RIG infiltration, or if unavoidable, sutures should be loose to allow optimal HRIG diffusion.

For previously immunised individuals of any age who have documented evidence of previous PrEP or at least 2 administrations of vaccine for PEP, HRIG is not indicated. If an individual has a repeat exposure 3 months after the last PEP, the PEP schedule for previously immunised individuals should be followed; RIG is not indicated.

Dose, route and schedule
The dose is 20 IU/kg. After thorough wound cleansing, HRIG should be infiltrated into the depth of the wound and around the wound as much as anatomically feasible. Any remainder should be injected IM at a site distant from that of the vaccine, e.g., anterolateral thigh or deltoid.

HRIG is not indicated if more than seven days have elapsed since commencement of active immunisation.

HRIG must only be used in combination with rabies vaccine.

Adverse reactions
Local: Very common: injection site pain, erythema, induration, pruritus.
General: Very common or common: headache, nausea, diarrhoea, myalgia, arthralgia, lymphadenopathy, abdominal pain, vomiting, urticaria, pruritus, dyspnoea, wheezing, dizziness.

Contraindications
Because of the life-threatening risk due to rabies, there are no contraindications to the administration of HRIG.

Precautions for use
HRIG must not administered into a blood vessel, because of the risk of shock.

HRIG contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may develop anaphylaxis after administration of blood components containing IgA.

Vaccine and HRIG suppliers
Both the vaccine and HRIG are available from Cherry Orchard Hospital (Tel. 076 695 5000).

Table 18.2 provides guidance on the post-exposure administration of rabies vaccine and HRIG following risk assessment

Table 18.2 Post-exposure treatment following risk assessment

Rabies risk (any age)	Unimmunised	Previously immunised
Category I exposure	Wash exposed skin No PEP required.	Wash exposed skin No PEP required.
Category II exposure	Wound washing and immediate vaccination: 1 dose IM on days 0, 3, 7 and day 14–28 (four doses) **HRIG is NOT indicated***	Wound washing and immediate vaccination: 1 dose IM days 0 and 3 (two doses) **HRIG is NOT indicated***
Category III exposure	Wound washing and immediate vaccination: 1 dose IM on days 0, 3, 7 and day 14–28 (four doses) **HRIG is recommended**	Wound washing and immediate vaccination: 1 dose days 0 and 3 (2 doses) **HRIG is NOT indicated***

*Those who are immunocompromised should receive HRIG.

Further information on rabies vaccine and post-exposure treatment is available from the Health Products Regulatory Authority (https://www.hpra.ie/), Cherry Orchard Hospital (Tel. 076 695 5000), and the Health Protection Surveillance Centre (https://www.hpsc.ie/)

Bibliography

American Academy of Paediatrics (2018). Red Book: Report of the Committee on Infectious Diseases. 31st ed. Elk Grove Village, IL: American Academy of Paediatrics.

Centers for Disease Control and Prevention (2018). Rabies. http://www.cdc.gov/rabies/

European Centre for Disease Prevention and Control. https://ecdc.europa.eu

Department of Health UK (2013). Immunisation against infectious disease (The Green Book). https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book#the-green-book

O'Brien K et al (2019). The WHO position on rabies immunization – 2018 updates. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6863036/

Public Health England (2018). Rabies post-exposure treatment: management guidelines. https://www.gov.uk/government/publications/rabies-post-exposure-prophylaxis-management-guidelines

World Health Organization (2018a) WHO Expert Consultation on Rabies: WHO TRS No 1012. Third report. http://www.who.int/rabies/resources/who_trs_1012/en/

World Health Organization (2018b) Rabies vaccines: WHO position paper. Weekly Epidemiological Record 2018, 93, 201-220 http://www.who.int/rabies/resources/who_wer9316/en/