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Rabies

NOTIFIABLE

The disease

Rabies is an acute viral encephalomyelitis caused by members of the lyssavirus genus. The disease may be caused by rabies virus genotype 1 (classical rabies) or less commonly by rabies-related lyssaviruses. The presentations are clinically indistinguishable. Rabies-related lyssaviruses implicated in human disease include European bat lyssaviruses (EBLVs) and Australian bat lyssavirus (ABLV).

Infection is usually via the bite or scratch of a rabid animal, most frequently a dog. In some parts of the world, other animals such as bats, cats and monkeys are important sources of exposure. In parts of Europe (including the UK) EBLV-1 and EBLV-2 are found in insectivorous bats and have occasionally caused human disease.

On rare occasions, transmission of the virus has occurred through body fluids from an infectious animal coming into contact with an individual's mucous membranes. Exposure through mucous membranes has a low probability of infection but must be managed as a significant event. Infection does not occur through intact skin. Virus is present in some tissues and fluids of humans with rabies, but person-to-person spread of the disease has not been documented other than in exceptional circumstances. Cases have occurred rarely outside the UK through corneal grafts and other transplanted tissues taken from individuals with rabies.

The incubation period is generally between three and 12 weeks, but may range from four days to 19 years. In more than 93% of patients, the onset is within one year of exposure. The onset of illness is insidious. Early symptoms may include paraesthesiae around the site of the wound, fever, headache and malaise. The disease may then present with hydrophobia, hallucinations and maniacal behaviour progressing to paralysis and coma, or as an ascending flaccid paralysis and sensory disturbance. Rabies is almost always fatal, death resulting from respiratory paralysis. There is no specific treatment other than supportive care once clinical symptoms develop.

History and epidemiology of the disease

Rabies in animals occurs in all continents except Antarctica, although individual countries are reported to be rabies-free. In the US, classical rabies virus in animals has become more prevalent since the 1950s; skunks, raccoons and bats account for 85% of animal cases. In Asia, Africa, Central and South America, rabies (classical rabies virus, genotype 1) is endemic in feral dogs. In Mexico and Central and South America, vampire bats carry the classical rabies virus. Some countries that are declared rabies-free have rabies-related viruses in their bat populations, for example Australia and the UK. In the UK, rabies-related viruses have only been detected in Daubenton's bats. The virus has never been detected in the commonest bat species, the pipistrelles. In other parts of Europe and in Australia, other bat species have been affected.

During the twentieth century, rabies in wildlife has spread through parts of Central and Western Europe. Foxes have been the main host, but many other animals have also been infected, particularly dogs and cats. The incidence of endemic, fox-adapted rabies in Western Europe fell dramatically in the last years of the twentieth century. This has been largely due to the vaccination of wild and domestic animals. Rabies continues to be reported in domestic animals imported from non-rabies-free countries. Rabies remains prevalent in Eastern Europe and Turkey.

In humans, between 40,000 and 70,000 cases of rabies occur each year worldwide (World Health Organization, 2001). Most cases are in developing countries, particularly India (Plotkin and Orenstein, 2004). In the UK, deaths from classical rabies continue to occur in people infected abroad. Such instances are, however, rare, with 24 deaths having been reported since 1902. None had received appropriate post-exposure prophylaxis. A considerable number of people present for medical advice on their return to the UK with a history of exposure to an animal abroad. In 2000, 295 such people received prophylaxis in England and Wales (Hossain *et al.*, 2004).

No case of indigenous human rabies from animals other than bats has been reported in the UK since 1902. In 2002, a man died from rabies caused by EBLV-2 acquired in the UK from a bat (Fooks *et al.*, 2003). Only three other cases of EBLV infection (all fatal) have been reported in the past 30 years in Europe (Nathwani *et al.*, 2003).

The rabies vaccination

There are currently two rabies vaccines licensed for use in the UK – human diploid cell vaccine (HDCV) (Rabies Vaccine BP Pasteur Merieux) and purified chick embryo cell rabies vaccine (PCEC) (Rabipur®). Other cell-culture-derived vaccines are available in other countries and include rabies vaccine viruses grown in Vero cells.

The vaccines available in the UK are thiomersal-free. The vaccines are inactivated, do not contain live organisms and cannot cause the disease against which they protect.

HDCV is a freeze-dried suspension of Wistar rabies virus strain PM/WI 38 1503-3M cultured in human diploid cells and inactivated by betapropiolactone. The potency of the reconstituted vaccine is not less than 2.5IU per 1.0ml dose. It contains traces of neomycin, and human albumin is used as an excipient. The PCEC rabies vaccine is a freeze-dried suspension of the Flury LEP-25 rabies virus strain cultured in chick embryo cells and inactivated with beta-propiolactone. The potency of the reconstituted vaccine is not less than 2.5IU per 1.0ml dose. It contains traces of amphotericin B, chlortetracycline and neomycin.

These vaccines may be used interchangeably to provide protection pre- or post-exposure.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Presentation

Rabies vaccines are white, lyophilised powder for reconstitution with the clear and colourless diluent supplied. The vaccines should only be reconstituted with the diluent supplied. On reconstitution Rabipur is a clear, colourless solution, and Rabies Vaccine BP is a pinkish-coloured solution.

They should be used immediately and no later than one hour after reconstitution with the diluent supplied.

Human rabies immunoglobulin (HRIG) should be stored in a refrigerator between +2˚C and +8˚C. These products are tolerant to ambient temperatures for up to one week. They can be distributed in sturdy packaging outside the cold chain if needed.

Dosage and schedule

For primary pre-exposure immunisation, three doses of 1.0ml of rabies vaccine should be given on days 0, 7 and 28. The third dose can be given from day 21 if there is insufficient time before travel.

Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

The Joint Committee on Vaccination and Immunisation recommends the intramuscular rather than the intradermal route for rabies vaccine. The use of the intradermal route is not covered by the manufacturers' product licence and, if it is used, this is at the doctor's own responsibility.

Rabies vaccines can be given at the same time as other vaccines, including other travel vaccines. The vaccines should be given at separate sites, preferably in different limbs. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records. The vaccinee must keep a record of the vaccine and regimen received as it will influence future treatment.

Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320).

Rabies-specific immunoglobulin

HRIG is obtained from the plasma of immunised and screened human donors. Donors are selected from countries where there are no known cases of vCJD, and their plasma is comprehensively deactivated. HRIG is used after exposure to rabies to give rapid protection until rabies vaccine, which should be given at the same time at a separate site, becomes effective.

Administration

When indicated for post-exposure prophylaxis (see below), HRIG 20IU/kg body weight should be infiltrated in and around the cleansed wound. If infiltration of the whole volume is not possible or the wound is healed or not visible, any remaining HRIG should be given intramuscularly in the anterolateral thigh (not gluteal region), remote from the vaccination site. If vaccine is given but HRIG treatment is delayed, HRIG should still be given up to seven days after starting the course of vaccine.

Disposal

HRIG is for single use and any unused solution should be disposed of by incineration at a suitably approved facility.

Recommendations for use of the vaccine

The aim of the rabies immunisation programme is to protect those who are at most risk of exposure to rabies.

Pre-exposure (prophylactic) immunisation

Pre-exposure immunisation with rabies vaccine should be offered to:

- laboratory workers handling the virus
- those who, in the course of their work, regularly handle imported animals, for example:
  - at animal quarantine centres
  - at zoos
  - at research and acclimatisation centres where primates and other imported animals are housed
  - at ports, e.g. certain HM Revenue and Customs officers
  - at the premises of carrying agents authorised to carry imported animals
- veterinary and technical staff in the State Veterinary Service; the Department for Environment, Food and Rural Affairs; the Scottish Executive Environment and Rural Affairs Department; the Welsh Assembly Government Environment, Planning and Countryside Department; and the Northern Ireland Department of Agriculture and Rural Development
- inspectors appointed by local authorities under the Animal Health Act (2002). This only includes those local authority dog wardens who are also inspectors. Other dog wardens have a low risk of exposure, and post-exposure prophylaxis in the event of an incident is appropriate

- people who regularly handle bats in the UK
- those working abroad (e.g. veterinary staff or zoologists) who by the nature of their work are at risk of contact with rabid animals
- health workers who are about to be at risk of direct exposure to body fluids or other tissue from a patient with probable or confirmed rabies.

Pre-exposure immunisation is also recommended for some travellers, including:

- those living in or travelling for more than one month to rabies-enzootic areas, unless there is reliable access to prompt, safe medical care (see below)
- those travelling for less than one month to enzootic areas but who may be exposed to rabies because of their travel activities, or those who would have limited access to post-exposure medical care.

Further information is available from the National Travel Health Network and Centre (www.nathnac.org.uk) and, in Scotland, from Health Protection Scotland (www.hps.scot.nhs.uk). Country-by-country advice is also contained in *Health information for overseas travel* (Department of Health, 2001). All travellers to enzootic areas should also be informed by their medical advisers of the practical steps to be taken if they are bitten by an animal or have some other types of exposure which puts them at risk of rabies.

A risk assessment should be undertaken when considering immunisation for children less than one year of age.

Reinforcing doses

For those at regular and continuous risk, a single reinforcing dose of vaccine should be given one year after the primary course has been completed. Further doses should be given at three- to five-year intervals thereafter. For those at intermittent risk or who are travelling again to rabies-enzootic areas without ready access to safe, medical care, a booster dose should be given, from two years after the primary course has been completed.

Serological testing is advised only for those who work with the live viruses. Such individuals should have their antibodies tested every three to six months, and be given reinforcing doses of vaccine as necessary to maintain their immune status. The World Health Organization (WHO) currently considers a minimal acceptable antibody titre to be 0.5IU/ml.

Post-exposure management

Post-exposure management normally consists of wound treatment and risk assessment for appropriate immunisation. Treatment and immunisation after a possible rabies exposure will depend on the circumstances of the exposure, including the local incidence of rabies in the species involved and the immune status of the person.

Wound treatment

As soon as possible after the incident, the wound or site of exposure (e.g. mucous membrane) should be cleaned by thorough flushing under a running tap for several minutes and washing with soap or detergent and water. A suitable disinfectant should be applied and the wound covered with a simple dressing.

Suitable disinfectants include 40 to 70% alcohol, tincture or aqueous solution of povidone-iodine, or quaternary ammonium compounds, for example cetrimide solution 0.15%.

Primary suture could cause further damage to the wound and may increase the risk of introduction of rabies virus to the nerves. It should be avoided or postponed.

Risk assessment

Each case requires a full, expert risk assessment based on the information outlined below. Advice on the assessment of the risk and appropriate management should be obtained from the Health Protection Agency (HPA) Centre for Infection, Colindale, London (Tel: 020 8200 6868); in Scotland from Health Protection Scotland (Tel: 0141 300 1100); and in Northern Ireland from the Public Health Laboratory, Belfast City Hospital (Tel: 028 9032 9241).

As much as possible of the following information must be collected:

The site and severity of the wound

High-risk exposures are those with broken skin, including single or multiple transdermal bites or scratches, or where mucous membranes or an existing skin lesion have been contaminated by the animal's saliva or other body fluid. Intact skin is a barrier against infection. Bites represent a higher risk than scratches. Proximal bites (e.g. face, fingers) represent a higher risk than distal wounds. Bat bites and scratches may not be visible.

The circumstances of the bite (or other contact)

An unprovoked attack carries a higher risk than one that is provoked.

The species, behaviour and appearance of the animal

A frantic or paralysed dog or cat represents a high risk of infection. The name and address of the owner of the animal should be obtained, if possible. The dog or cat should be observed for 15 days to see if it begins to behave abnormally; the relevant period is not known for animals other than cats and dogs. If the dog or cat is feral or stray and observation is impossible, try to contact a local doctor or veterinarian who may know whether rabies occurs in the locality. Bat rabies may be suspected if the bat is sick or grounded without injury, or if an uninjured bat is found dead. Apparently healthy bats may have rabies.

The vaccination status of the animal

A regularly vaccinated animal is unlikely to be rabid but, rarely, vaccinated dogs have transmitted rabies.

The origin of the animal, the location of the incident and the incidence of rabies in that species

It is important to know whether the implicated animal is indigenous to that locality or originates elsewhere, and to ascertain the incidence of rabies in the originating area. If necessary, the assistance of local veterinary officials should be sought or advice should be taken from a local doctor.

Terrestrial animals (not bats)

The risk of rabies by country and territory, as of the time of writing, is provided below. This list covers all popular destinations but is not exhaustive and may become out of date. For updated information on rabies by country, see WHO's *Rabies Bulletin Europe* (www.who-rabies-bulletin.org), or the epidemiology website of the Centers for Disease Control and Prevention (CDC), USA (www.cdc.gov/ncidod/dvrd/rabies/epidemiology/epidemiology.htm).

- **No risk**: Animals originating from the following countries and territories are considered to pose 'no risk' of rabies (free of terrestrial rabies):
  - **Europe**: Belgium, Cyprus, Denmark, Faroe Islands, Finland, France, Gibraltar, Greece, Iceland, Ireland, Italy (except the northern and eastern border regions), Luxembourg, Malta, the Netherlands, Norway (mainland), Portugal, Spain (mainland, excluding North African coast territories) and the Canary Islands, Sweden and the UK.

- **Americas**: Anguilla, Antigua and Barbuda, Bahamas, Barbados, Bermuda, the British Virgin Islands, the Cayman Islands, Dominica, the French Antilles, Guadaloupe, Jamaica, Martinique, Montserrat, Netherlands Antilles, St Christopher and Nevis, St Lucia, St Martin, St Pierre and Miquelon, St Vincent and the Grenadines, the Turks and Caicos Islands, the Virgin Islands and Uruguay
- **Asia**: Bahrain, Brunei Darussalam, Hong Kong, Japan, Kuwait, the Maldives, Qatar, Singapore, Taiwan and the United Arab Emirates
- **Oceania**: American Samoa, Australia, the Cook Islands, Federated States of Micronesia, Fiji, French Polynesia, Guam, Kiribati, the Marshall Islands, New Caledonia, New Zealand, Niue, the Northern Mariana Islands, Palau, Papua New Guinea, Samoa, Sao Tome and Principe, the Solomon Islands, Tonga, Vanuatu and Western Samoa.

- **Low risk**: Animals originating from the following countries and territories are considered to pose a 'low risk' of rabies:
  - **Europe**: Austria, Bulgaria, the Czech Republic, Germany and Switzerland
  - **Americas**: Canada, USA (CDC, Atlanta provides information on the risk of rabies in different parts of the USA).
- **High risk**: Animals originating from the following countries, where terrestrial rabies is enzootic, are considered 'high risk':
  - Colombia, Cuba, the Dominican Republic, Ecuador, El Salvador, Guatemala, India, parts of Mexico, Nepal, Pakistan, Peru, Philippines, Sri Lanka, Thailand, Turkey and Vietnam.

Countries in Asia, Africa and South America not otherwise mentioned as 'no risk' or 'low risk' should be considered as 'high risk'.

Bats

Both classical rabies virus and rabies-related lyssaviruses may be acquired from bats depending on the species and origin. Information on the local epidemiology of rabies in bats should be sought.

Following a case of EBLV infection in a bat handler in the UK, bat exposures are an increasing cause for concern. Assessment of the risk from a possible bat contact is more difficult than for a terrestrial animal. Transmission of EBLV can occur in the absence of a recognised contact (e.g. waking to find a bat in the room). Information that is required for an accurate risk assessment includes:

- the nature of the contact, e.g. a definite bite or scratch, handling or touching, or a possible unrecognised exposure
- origin and condition of the bat, e.g. species and behaviour of the bat. If the species of the bat is unknown, then size and location may help to determine the most likely type. If the bat is available, urgent testing can be arranged
- severity and site of the wound.

Advice should be sought from the HPA, Virus Reference Department, Colindale, London (Tel: 020 8200 4400) or Communicable Disease Surveillance Centre (Tel: 020 8200 6868) in England and Wales; Health Protection Scotland (Tel: 0141 300 1100) in Scotland; or the Public Health Laboratory, Belfast City Hospital (Tel: 028 9032 9241) in Northern Ireland.

Post-exposure immunisation and immunoglobulin

Treatment, including cleaning the wound as above, must not be delayed, and should be started as soon as possible while enquiries are made about the local epidemiology of rabies in the country concerned (see above) and, where possible, the ownership and condition of the biting animal.

As the incubation period for rabies can be prolonged, treatment should still be considered even if the interval from exposure is lengthy. Specialist advice should be sought (as above).

Contraindications

Pre-exposure rabies vaccine should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of rabies vaccine, or
- a confirmed anaphylactic reaction to any component of the vaccine.

There are no absolute contraindications to post-exposure rabies vaccine. In the event of a hypersensitivity reaction to a dose of a pre-exposure course, such individuals should still receive post-exposure vaccination if indicated, because the risks of rabies outweigh the risks of hypersensitivity. When a hypersensitivity reaction occurs during post-exposure immunisation, further doses should be given under close medical supervision.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone pre-exposure immunisation.

Table 27.1 Guide to post-exposure prophylaxis following risk assessment

	Post-exposure prophylaxis	
Rabies risk	**Unimmunised /incompletely immunised individual***	**Fully immunised individual**
No risk	None	None
Low risk	Five doses (each 1ml) rabies vaccine on days 0, 3, 7, 14 and 30	Two doses (each 1ml) rabies vaccine on days 0 and 3
High risk	Five doses (each 1ml) rabies vaccine on days 0, 3, 7, 14 and 30, plus HRIG on day 0 only	Two doses (each 1ml) rabies vaccine on days 0 and 3

* Persons who have not received a full course of pre- or post-exposure tissue culture rabies vaccine.

If an individual is acutely unwell, pre-exposure immunisation should be postponed until they have recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Pregnant women and breast-feeding

Pregnant women and breast-feeding mothers should only be given pre-exposure vaccination if the risk of exposure to rabies is high and rapid access to post-exposure prophylaxis would be limited. Post-exposure treatment should be given to pregnant women when indicated.

The single site, intradermal 0.1ml pre-exposure vaccine regimen should not be used in those taking chloroquine for malaria prophylaxis, as this suppresses the antibody response.

Immunosuppression and HIV infection

Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given rabies vaccines in accordance with the recommendations above. These individuals may not make a full antibody response. Re-immunisation should be considered after treatment is finished and recovery has occurred.

Individuals who are immunosuppressed or with HIV who are exposed may require a different regime for post-exposure management. Specialist advice should be sought urgently.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk) the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.bhiva.org/chiva).

Adverse reactions

Rabies vaccine may cause local reactions such as redness, swelling or pain at the site of injection within 24 to 48 hours of administration. Systemic reactions such as headache, fever, muscle aches, vomiting and urticarial rashes are rare. Delayed hypersensitivity reactions have been reported from the US. Reactions may become more severe with repeated doses. Neurological conditions, such as Guillain-Barré syndrome, have been reported extremely rarely; a causal association with vaccination is not established.

HRIG may cause local pain and low-grade fever, but no serious adverse reactions have been reported.

All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccines labelled with a black triangle (▼), should be reported to the Commission on Human Medicines using the Yellow Card scheme. Serious suspected adverse reactions to vaccines in adults should also be reported through the Yellow Card scheme.

Management of cases

Human rabies is a notifiable disease. In the event of a case of human rabies, the Consultant in Communicable Disease Control (in England, Wales or Northern Ireland) or the Consultant in Public Health Medicine for Communicable Disease and Environmental Health (in Scotland) should be informed.

Supplies

- Rabies Vaccine BP is available from Sanofi Pasteur MSD (Tel: 0800 085 5511).
- Rabipur is available from Novartis Vaccines (Tel: 08457 451500) or MASTA (Tel: 0113 238 7500) .

Rabies vaccine for pre-exposure immunisation of those at occupational risk and bat handlers is supplied by the Department of Health and should be obtained from the HPA Virus Reference Department (Tel: 020 8200 4400). For others, it can be obtained through local pharmacies by private prescription. In Scotland, the vaccine is available through normal GP channels.

For post-exposure use, vaccine is supplied by centres listed in the HPA directory. Information may be obtained from the HPA Virus Reference Department (Tel: 020 8200 4400) or Communicable Disease Surveillance Centre (Tel: 020 8200 6868) in England; the National Public Health Service (Virology Cardiff) for Wales (Tel: 029 2074 7747); Health Protection Scotland (Tel: 0141 300 1100); and the Public Health Laboratory, Belfast City Hospital (Tel: 028 9032 9241) in Northern Ireland.

HRIG is manufactured by Bio Products Laboratory and supplied through the HPA for England. Supply centres for rabies vaccine and HRIG are listed in the Department of Health's *Memorandum on rabies: prevention and control* (www.dh.gov.uk – enter title in the search box).

Rabies vaccine and HRIG for use in post-exposure treatment are available free of charge to patients. If vaccine held for pre-exposure prophylaxis is used for post-exposure treatment, it will be replaced free of charge.

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