

PART 3: VACCINES LISTED BY DISEASE

3.1 AUSTRALIAN BAT LYSSAVIRUS INFECTION AND RABIES

Virology

Australian bat lyssavirus (ABL) and rabies virus are members of the family Rhabdoviridae, genus *Lyssavirus*. There are 7 known genotypes within the genus *Lyssavirus*; ABL (genotype 7) is more closely related to rabies virus (genotype 1) than any of the other 6 genotypes.

Clinical features

Based on the 2 recognised human cases of ABL infection, it has to be assumed that ABL has the same clinical features as rabies. The incubation period of rabies is usually 3 to 8 weeks, but can range from as short as a week to, on rare occasions, several years. The risk of rabies is higher, and the incubation period shorter, after severe and multiple wounds proximate to the central nervous system (such as on the head and neck) and in richly innervated sites (such as the fingers).

Typically, in the prodromal phase of rabies, which lasts up to 10 days, the patient may experience non-specific symptoms such as anorexia, cough, fever, headache, myalgia, nausea, sore throat, tiredness and vomiting.¹ Paraesthesiae and/ or fasciculations at or near the site of the wound may be present at this stage. Anxiety, agitation and apprehension may also occur.

Most rabies patients present with the furious or encephalitic form.¹ In the encephalitic phase, objective signs of nervous system involvement include aerophobia, hydrophobia, bizarre behaviour, disorientation and hyperactivity. Signs of autonomic instability such as hypersalivation, hyperthermia and hyperventilation may occur.¹ The neurological status of the patient deteriorates over a period of up to 12 days, and the patient either dies abruptly from cardiac or respiratory arrest, or lapses into a coma. Rabies is almost invariably fatal.

Epidemiology

Rabies is endemic throughout much of Africa, Asia, the Americas and Europe, where the virus is maintained in certain species of mammals.¹ Australia, New Zealand, Japan, Papua New Guinea and Pacific Island nations are free of endemic rabies but it must be remembered that this can change at any time. For example in 2008, rabies was reported in dogs on the island of Bali, Indonesia. Prior to this, Bali was considered to be free of rabies although rabies was known to occur in other areas of Indonesia. Human rabies characteristically follows a bite from a rabid animal, most frequently a dog, but in some parts of the world, other animals, such as jackals and bats, are important sources of exposure. In countries where rabies vaccination of domestic animals is widespread (North America and Europe), wild animals such as raccoons and foxes are important reservoirs.¹

Cases of rabies after animal scratches, the licking of open wounds or saliva contact with intact mucous membranes are very rare.^{2,3} Cases have been recorded after exposure to aerosols in a laboratory and in caves infested with rabid bats, and cases have been reported following tissue transplantation from donors who died with undiagnosed rabies.¹

Although rabies in travellers is rare, such cases – always fatal – continue to be reported in the medical literature.^{4,5} Travellers to rabies-endemic regions should be advised of the risk and to avoid close contact with either wild or domestic animals; this is particularly important for children. They should be advised about pre-travel (ie. pre-exposure) rabies vaccination (or, if appropriate, booster doses), and they should be advised on what to do should they be either bitten or scratched by an animal while abroad.

In Australia, 2 cases of a fatal rabies-like illness caused by ABL have been reported, one in 1996 and the other in 1998.⁶ Both patients had been bitten by bats. Evidence of ABL infection has since been identified in all 4 species of Australian fruit bats (flying foxes) and in several species of Australian insectivorous bats. It should therefore be assumed that all Australian bats have the potential to be infected with ABL.

Rabies vaccine

- **Mérieux Inactivated Rabies Vaccine** – Sanofi Pasteur Pty Ltd. Each 1.0 mL monodose vial of lyophilised vaccine contains at least 2.5 IU inactivated rabies virus; 100–150 µg neomycin; ≤70 mg human serum albumin; trace of phenol red (indicator). 1.0 mL distilled water as diluent.
- **Rabipur Inactivated Rabies Virus Vaccine** – CSL Biotherapies/Novartis Vaccines. Each 1.0 mL monodose vial of lyophilised vaccine contains at least 2.5 IU inactivated rabies virus; trace amounts of neomycin, chlortetracycline and amphotericin B; may contain trace amounts of bovine gelatin. May contain traces of egg protein. 1.0 mL distilled water as diluent.

The Mérieux vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus that has been cultured on human diploid cells and then inactivated by beta-propiolactone. This human diploid cell vaccine (HDCV) is coloured off-white, but after reconstitution with the diluent it turns a pinkish colour due to the presence of phenol red. The vaccine does not contain a preservative.

Rabipur is a lyophilised, stabilised suspension of inactivated Flurey LEP rabies virus that has been cultured on purified chick embryo cells and then inactivated by beta-propiolactone. This purified chick embryo cell vaccine (PCECV) does not contain a preservative.

The above two vaccines, and other tissue culture vaccines, are interchangeable.

Rabies immunoglobulin

- **Imogam Rabies** – Sanofi Pasteur Pty Ltd (human rabies immunoglobulin). Each 1.0 mL contains IgG class human rabies antibodies with a minimum titre of 150 IU; 22.5 mg glycine; 1 mg sodium chloride. It is supplied in 2 mL and 10 mL vials.

Human rabies immunoglobulin (HRIG) is prepared by cold ethanol fractionation from the plasma of hyperimmunised human donors.

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.⁷ Rabies vaccine, diluent and HRIG should be transported and stored at +2°C to +8°C. Do not freeze. Reconstituted vaccine should be used immediately after reconstituting. The HRIG should be used immediately once the vial is opened.

Dosage and administration

NB. The doses of rabies vaccines are the same for both children and adults.

(i) Pre-exposure prophylaxis

The dose of rabies vaccine for pre-exposure prophylaxis is 1.0 mL by IM injection, on days 0, 7 and 28. (HDCV can also be given by the subcutaneous (SC) route.)

(ii) Post-exposure treatment

The dose of rabies vaccine for post-exposure treatment is 1.0 mL by IM injection, on days 0, 3, 7, 14 and 28–30. (HDCV can also be given by the SC route.) The dose of HRIG is 20 IU/kg body mass by infiltration around the wounds; the remainder of the dose should be administered by IM injection.

Recommendations

(i) Pre-exposure prophylaxis for Australian bat lyssavirus infection and rabies

Rabies vaccine is effective and safe when used for pre-exposure prophylaxis for rabies.⁸ Although data on the effectiveness of rabies vaccine as prophylaxis against ABL infection are limited, the available animal data⁹ and clinical experience support its use. Pre-exposure prophylaxis simplifies the management of a subsequent exposure because fewer doses of vaccine are needed and because HRIG is not required. (Rabies immunoglobulin is often difficult, or even impossible, to obtain in many developing countries.)

Pre-exposure prophylaxis with rabies vaccine is recommended for:

- people in Australia liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats),
- expatriates and travellers who will be spending prolonged periods (ie. more than a month) in rabies-endemic areas. (NB. This time interval, of more than a month, is arbitrary, and rabies has occurred in travellers following shorter periods of travel),⁵
- people working with mammals in rabies-endemic areas, and
- research laboratory personnel working with live lyssaviruses.

Pre-exposure prophylaxis for both ABL infection and rabies, for all ages, consists of a total of 3 IM (IM or SC if HDCV is used) injections of 1 mL of rabies vaccine, the second given 7 days after the first, and the third given 28 days after the first. Although the third dose can be given at 21 days,¹ there are no data to support the use of an even more accelerated schedule for those with limited time before travel to a rabies endemic area.

Doses should be given in the deltoid area, as rabies neutralising antibody titres may be reduced after administration in other sites. In particular, vaccine should never be given in the buttock, as failure of pre-exposure prophylaxis has been reported when given by this route.

Because the antibody response is reported as satisfactory after the pre-exposure prophylaxis regimen, routine serological testing to confirm seroconversion is not necessary. However, people with impaired immunity who are at risk of exposure to ABL or rabies should have their antibody titres determined 2 to 3 weeks after the third dose of vaccine.

Booster doses of rabies vaccine are recommended for immunised people who have ongoing exposure to either ABL or rabies. People who work with live lyssaviruses in research laboratories should have rabies antibody titres measured every 6 months. If the titre is reported as inadequate (<0.5 IU/mL), they should have a booster dose. Others with occupational exposures to bats in Australia, and those who are likely to be exposed to potentially rabid animals in endemic countries, should have rabies antibody titres measured every 2 years. If the titre is reported as inadequate, they should have a booster dose. Alternatively, a booster dose may be offered every 2 years without determining the antibody titre.

Intradermal pre-exposure prophylaxis

There are no data on the protection provided by intradermal (ID) rabies vaccination for the prevention of ABL infection. Therefore, *ID pre-exposure administration of rabies vaccine should not be used for pre-exposure prophylaxis of ABL.*

Antibody titres are lower and wane more rapidly after ID compared to either IM or SC administration of rabies vaccine, and there may be a slow initial immune

response following exposure to rabies virus in those given ID rabies vaccine.¹⁰ For these 2 reasons, it is strongly recommended that the IM (IM or SC if HDCV is used) route be used for pre-exposure prophylaxis.

However, the cost of IM (IM or SC if HDCV is used) rabies vaccination may be prohibitive for some travellers. In this circumstance, ID rabies vaccination, using a dose of 0.1 mL on days 0, 7 and 28, may be considered, provided that:

- it is given by those with not only expertise in, but also regular practice of, the ID technique,
- it must not be administered to anyone known to have impaired immunity,
- it must not be administered to those taking either chloroquine or other antimalarials structurally related to chloroquine (eg. mefloquine) at either the time of, or within a month following, vaccination,
- any remaining vaccine is discarded at the end of the session during which the vial is opened, and
- the rabies antibody level should be checked 2 to 3 weeks following completion of the pre-exposure course of ID vaccine.

The use of the ID route for rabies vaccination is the practitioner's own responsibility, as rabies vaccines are not licensed for use via this route in Australia. The ID route should never be used to administer rabies vaccine by practitioners who only occasionally provide travel medicine services.

(ii) Post-exposure treatment for Australian bat lyssavirus and rabies exposures

Rabies vaccine and HRIG are effective and safe when used for post-exposure treatment following rabies exposures. Although data on the effectiveness of rabies vaccine and HRIG as post-exposure treatment against ABL infection are limited, the available animal data⁹ and clinical experience support its use. The essential components of post-exposure treatment for either ABL or rabies exposures are prompt local wound management and, for people who have not previously been vaccinated, administration of HRIG and rabies vaccine as soon as is practicable.⁸ Both HRIG and rabies vaccine are available for post-exposure treatment from the relevant State/Territory health authorities (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

Post-exposure treatment should be considered whenever a bite, scratch or mucous membrane exposure to saliva from any Australian bat has occurred, regardless of the extent of the bite or scratch, the time lapsed since the exposure, the species of bat involved, and even if the bat was apparently normal in appearance and behaviour. (Although ABL is more likely to be found in bats that either appear unwell or are behaving abnormally,¹¹ it has to be assumed that any bat is potentially infected with ABL.)

However, exposure to bat blood, urine or faeces, or to a bat that has been dead for more than 4 hours, does not warrant post-exposure treatment.

Where post-exposure treatment for a potential exposure to ABL is indicated, the bat should, if possible, without placing others at risk of exposure, be kept and arrangements promptly made for testing by the relevant State/Territory veterinary or health authority. Following the wound management, the administration of HRIG and rabies vaccine can be withheld if the result (concerning the bat's ABL status) will be available within 48 hours of the exposure; if the result will not be available within 48 hours, full post-exposure treatment should begin as soon as is practicable. Where a bat is tested at a reference laboratory and later found to be negative for ABL, then post-exposure treatment for individuals exposed to that bat can be discontinued.

The relevant State/Territory health authority should be contacted about any animal bite or scratch sustained in a rabies-endemic area. Dogs and monkeys comprise the usual exposures in Asia, Africa and Central and South America, but exposures to other mammals must also be assessed for potential rabies transmission. If a traveller presents >10 days after being bitten or scratched by either a dog or cat in an endemic country, and it can be reliably ascertained that the animal has remained healthy (>10 days after the exposure), post-exposure treatment is not required;^{8,12} otherwise, a complete course of treatment should be administered, even if there has been a considerable delay in reporting the incident.

Immediate and thorough washing of all bite wounds and scratches with soap and water, and the application of a virucidal preparation such as povidone-iodine solution after the washing, is an important measure in the prevention of ABL infection and rabies.¹ Consideration should be given at this stage of wound management to the possibility of tetanus and other wound infections, and appropriate measures taken. Primary suture of a bite from a potentially rabid animal should be avoided. Bites should be cleaned, debrided and well infiltrated with HRIG (see below).

a) Use of rabies vaccine in post-exposure treatment

Following the local wound management, the subsequent post-exposure treatment for either ABL or rabies exposures consists of: (i) a total of 5 doses of 1.0 mL of rabies vaccine given by IM (IM or SC if HDCV is used) injection; and (ii) HRIG (see below).

The volume of rabies vaccine administered to infants and children is the same as that given to adults (ie. 1.0 mL). The first dose of vaccine is given as soon as is practicable (day 0), and subsequent doses are given on days 3, 7, 14 and 28–30; deviations of a few days from this schedule are probably unimportant.⁸ In adults and children, the vaccine should be administered into the deltoid area, as administration in other sites may result in reduced neutralising antibody titres.

In infants <12 months of age, administration into the anterolateral aspect of the thigh is recommended.

Serological testing to measure response is unnecessary except in unusual circumstances, such as when the patient is known to have impaired immunity. In such cases, the antibody titre should be measured 2 to 3 weeks after the dose given at 28–30 days and a further dose given if the titre is reported as inadequate.

b) Use of rabies immunoglobulin in post-exposure treatment

Rabies has occurred in people who have received post-exposure rabies vaccine without rabies immunoglobulin being infiltrated in and around the wound.¹³ Therefore, *post-exposure treatment should always include the infiltration of HRIG in and around wounds at the same time as the first dose of rabies vaccine*, the only exceptions being people with documented evidence of either completion of the pre-exposure prophylaxis regimen or adequate rabies antibody titres. These people should receive vaccine only (see below).

A single dose of HRIG is given to provide localised anti-rabies antibody protection while the patient responds to the rabies vaccine. It should be given at the same time as the first post-exposure dose of vaccine (day 0). If not given with the first vaccine dose, it may be given up to day 7, but should not be given any later in the vaccination course. From day 8 onwards, an antibody response to rabies vaccine is presumed to have occurred.

The dose of HRIG for all age groups is 20 IU per kg body mass. HRIG should be *infiltrated in and around all wounds using as much of the calculated dose as possible*, and the remainder administered intramuscularly at a site away from the injection site of rabies vaccine. If the wounds are severe and the calculated volume of HRIG is inadequate for complete infiltration of all wounds (eg. extensive dog bites in a young child), the HRIG should be diluted in saline to make up an adequate volume for the careful infiltration of all wounds.

However, many bat bites occur as small puncture wounds on the fingers;⁸ such exposures are probably high-risk exposures because of the extensive nerve supply to the fingers and hand. Therefore, although infiltration of HRIG into finger wounds is likely not only to be technically difficult but also to be painful for the recipient, it must be undertaken. As much of the calculated dose of HRIG as possible should be infiltrated into finger and hand wounds using either a 25 or 26 gauge needle. To avoid the development of a compartment syndrome, the HRIG should be infiltrated very gently, and should not cause the adjacent finger tissue to go frankly pale or white. If necessary, a ring-block using a local anaesthetic may be required.

Table 3.1.1: Summary of Australian bat lyssavirus and rabies post-exposure treatment for non-immune individuals

Treatment	Immediate (Day 0)	Follow-up
Local treatment	Thorough wound cleansing	
Rabies vaccine	1.0 mL	1.0 mL on days 3, 7, 14, 28–30
Human rabies immunoglobulin (150 IU/mL)	20 IU/kg – no later than 7 days after the first rabies vaccine dose	Do not give later than 7 days after the first rabies vaccine dose

c) Post-exposure treatment of previously vaccinated people

People who have either completed a recommended course of pre-exposure prophylaxis, or previous post-exposure treatment, or who have documented adequate rabies neutralising antibodies, require a modified post-exposure treatment regimen if potentially exposed to either rabies virus or ABL. Local wound management as described above must be carried out, and a total of 2 doses of rabies vaccine (1.0 mL each) should be given by IM (IM or SC if HDCV is used) injection on day 0 and day 3. HRIG is not necessary in these cases.

In cases where the vaccination status is uncertain because the documentation of a full course of rabies vaccine is not available, the standard post-exposure treatment regimen (HRIG plus 5 doses of rabies vaccine) should be administered.

d) Post-exposure treatment commenced overseas

Australians travelling abroad who are exposed to a potentially rabid animal may be given post-exposure treatment with vaccines not available in Australia. However, it is very likely that they will receive a cell culture derived vaccine, all of which (including both vaccines available in Australia) are considered interchangeable.¹⁴

Therefore, if a person has received a cell culture-derived vaccine abroad, the standard post-exposure treatment regimen should be continued in Australia with either HDCV or PCECV. If the post-exposure treatment was started overseas but HRIG was not given, and the person presents in Australia within 7 days of commencing post-exposure treatment, HRIG should be given as soon as is practicable (and within 7 days of the first rabies vaccine). If the person presents in Australia 8 days or more after commencing post-exposure treatment, then HRIG should be withheld.

Contraindications

There are no contraindications to post-exposure treatment in a person with a possible exposure to either ABL or rabies.

A person with an anaphylactic sensitivity to eggs, or to egg proteins, should not receive PCECV; HDCV should be used instead.

Adverse events

Cell culture-derived vaccines are generally well tolerated. In a large study, the following adverse events were reported after administration of HDCV to adults: sore arm (15 to 25% very common), headache (5 to 8% common), malaise, nausea or both (2 to 5% common); and allergic oedema (0.1% uncommon).¹⁴ Similar adverse event profiles have been reported for the PCECV; these reactions occur at the same rates in children.¹⁴

Although anaphylactic reactions are rare (approximately 1 per 10 000 vaccinations) following administration of HDCV, approximately 6% (common) of people receiving booster doses may experience allergic reactions.¹⁴ The reactions typically occur 2 to 21 days after a booster dose, and are characterised by generalised urticaria, sometimes with arthralgia, arthritis, oedema, nausea, vomiting, fever and malaise. These reactions are not life-threatening; they have been attributed to the presence of beta-propiolactone-altered human albumin in the implicated vaccines.¹⁴ NB. HDCV contains human albumin, whereas PCECV does not.

Management of adverse events

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local reactions or mild systemic reactions. Such reactions can usually be managed with simple analgesics.

Because ABL infection and rabies are lethal diseases, the recommended vaccination regimens, in particular the post-exposure treatment regimen, should be continued even if a significant allergic reaction occurs following a dose of rabies vaccine. Antihistamines can be administered in an attempt to ameliorate any subsequent reactions. A patient's risk of developing either ABL infection or rabies must be carefully considered before deciding to discontinue vaccination.

Use of steroids and immunosuppressive agents

Corticosteroids and immunosuppressive agents can interfere with the development of active immunity and, therefore, if possible, should not be administered during post-exposure treatment. A person who either has an immunosuppressing illness or is taking immunosuppressant medications should have his/her rabies antibody titres checked 2 to 4 weeks after completion of the vaccination regimen (see above).

Use in pregnancy

Pregnancy is never a contraindication to rabies vaccination. Follow-up of 202 Thai women vaccinated during pregnancy did not indicate either increased medical complications or birth defects.¹⁵

Variations from product information

Neither of the product information sheets (of the 2 vaccines available in Australia) mentions that they can be used for both pre-exposure prophylaxis and post-exposure treatment for ABL exposures.

The HDCV product information recommends a routine sixth dose at 90 days in the post-exposure treatment regimen. This dose is not considered necessary on a routine basis but a further dose should be offered to a person with impaired immunity who has an inadequate antibody level following the standard regimen. It also recommends a pre-exposure booster after a year; boosters are usually recommended in Australia after 2 years (see above).

Rabies in Indonesia

Rabies has been documented in parts of Indonesia for some time, including the islands of Flores, Sulawesi, Sumatra, Ambon and Kalimantan. However, until late 2008, no cases had been reported in Bali. From late 2008, animal cases of rabies have been reported in Bali. Post-exposure treatment is necessary for any animal bite or scratch sustained in Indonesia including Bali. Any doubts or concerns about the need for post-exposure treatment following animal bites should be discussed with the State/Territory public health authority.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.