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Rabies

Prevention in travellers

This article forms part of our travel medicine series for 2010, providing a summary of prevention strategies and vaccination for infections that may be acquired by travellers. The series aims to provide practical strategies to assist general practitioners in giving travel advice, as a synthesis of multiple information sources which must otherwise be consulted.

Background

Rabies is an acute, almost invariably fatal, progressive encephalomyelitis caused by neurotropic lyssaviruses of the Rhabdoviridae family.

Objective

Rabies prevention, vaccines and postexposure prophylaxis are discussed, and information regarding vaccines, immunoglobulin products and vaccine regimens that may be encountered overseas is also given.

Discussion

Rabies viruses are present in most parts of the world, although it is mainly a problem in developing countries with more than 50 000 people dying from rabies each year, usually after a dog bite. All travellers require education regarding rabies prevention if travelling to an endemic area, and those at high risk of exposure should be offered pre-exposure vaccination.

Keywords: travel; preventive medicine; immunisation; communicable diseases; rabies



There are seven known genotypes within the genus Lyssavirus; all cause rabies-like illnesses. Rabies virus is genotype 1. Australian bat lyssavirus (ABL) is genotype 7, and is more closely related to rabies virus than the other genotypes.³⁻⁵

Rabies virus is present in the saliva of an infected animal and can be transmitted via animal bite, and rarely, via other exposures such as scratches to skin, licks to open wounds or mucous membranes, or after organ transplantation.^{5,6} Rather than entering the bloodstream, the highly neurotropic virus⁷ is taken up at nerve synapses and travels to the brain along the nerve by retrograde axoplasmic flow. Symptoms start once the brain is reached and viral replication occurs within neurons. The density of nerve endings in the bitten area, the proximity of the bite site to the central nervous system (CNS), and the severity of the bite, determines how quickly the virus is taken up into the nerve and travels to the brain to cause rabies encephalitis. Extensive bites to the face (close to the CNS) and hands (richly innervated areas) are considered the highest risk exposures.^{3,4}

Clinical features

The incubation period varies according to exposure site and severity, and can range from 1–12 weeks to several years.^{3,4}

Prodromal symptoms are nonspecific³ and include: fever, anorexia, cough, headache, myalgia, sore throat, tiredness and vomiting, as well as anxiety, agitation and apprehension. Paraesthesiae and/or fasciculations in proximity of the wound may occur.⁴

The disease then progresses, most commonly to the classic form of 'furious' encephalitic rabies with a progressively deteriorating neurological status and symptoms such as aerophobia, hydrophobia (where spasms of swallowing muscles are triggered by the sight, sound or perception of water),³ disorientation, and bizarre or hyperactive

Rabies is an acute, progressive encephalomyelitis caused by neurotropic lyssaviruses of the Rhabdoviridae family. Untreated, rabies is almost invariably fatal and has the highest fatality rate of all known human viral pathogens.¹ Over 50 000 people die of rabies each year, mostly in developing countries. Half of these fatalities occur in India.^{1,2} The first written description of rabies was found in the writings of the Babylonians, and it was known to exist in 1000 BC in Mesopotamia and Egypt,² in China in 500 BC, and India in 100 BC. In 1885, Louis Pasteur first prevented human rabies using postexposure vaccination.²

behaviour. Signs of autonomic instability such as hypersalivation, hyperthermia and hyperventilation may also occur. Death occurs within 12 days, usually from cardiac or respiratory arrest or after a period of coma.

Paralytic or ‘dumb’ rabies occurs in 30% of cases; it is less distinctive and more protracted, involving loss of sensation, weakness, pain and progressive flaccid paralysis, and may be misdiagnosed. There is no specific treatment of rabies once clinical signs have developed, and death is an almost universal outcome (extremely rarely, patients have survived rabies-like illnesses after extensive intensive care).^{3,4}

Epidemiology

Ninety-five percent of rabies victims reside in Asia or Africa; of these, over 99%^{2,5,8} contract the disease via dog bite,^{9,10} and 80% of cases occur in rural areas.⁵ In developed countries, rabies continues mainly in wild animals (bats, raccoons, foxes, jackals and wolves; occurrence of rabies in livestock and horses is very rare).¹¹ Rabies is endemic throughout much of Asia, Africa, Europe and the Americas (Figure 1). It is not endemic in Australia, Papua New Guinea, New Zealand, Japan and Pacific Island nations.⁴ However, bat lyssaviruses exist in Australia, and two cases of fatal rabies-like illnesses were reported in 1996 and 1998 following bat bites.^{3,4}

Countries at greatest risk are India, Nepal, Sri Lanka, Thailand, the Philippines, Vietnam, El Salvador, Guatemala, Peru, Columbia and Ecuador.¹² Rabies has been reported in Indonesian regions outside Bali including the islands of Flores, Sulawesi, Sumatra, Ambon and Kalimantan.⁴

What is the risk to travellers?

The risk of rabies is proportional to the traveller’s contact with potentially rabid animals, usually street dogs, but also monkeys and other mammals, mainly bats and cats. Veterinarians and people working with dogs and bats are at greatest risk. Children have a greater risk of rabies exposure than adults; they are more likely to pat animals, are less likely to report bites, and are more likely to have severe bites to the head, face and hands. Travellers with extensive outdoor exposure especially in rural areas, such as cyclists, trekkers, runners and campers, are also at increased risk, regardless of duration of travel.¹³ Travellers to tourist resorts tend

to be at very low risk.

Every month, 0.2–0.4% of travellers to developing countries experience an animal bite.¹⁴ The overall approximate estimated risk of rabies exposure in travellers is 16–200 per 100 000,³ and cases continue to be reported.⁴ Knowledge about rabies risk among travellers is often poor.^{15,16} Appropriate education regarding prevention and pre-exposure prophylaxis tends to be given preferentially to longer term travellers,¹⁷ although in a recent study 50% of travellers reporting animal associated injuries had travelled for less than 1 month, and 85% for less than 3 months.^{18–20} Other data suggest that risk for expatriates is approximately three times that of short term travellers and is often combined with poor access to correctly administered postexposure prophylaxis (PEP),²¹ which is unreliable or delayed in many rabies endemic countries.¹⁹ Despite this, a recent study has shown overall uptake of rabies pre-exposure prophylaxis, when recommended by a medical advisor, to be less than 50%.¹⁸

Prevention in travellers

All travellers should be advised to avoid approaching stray animals; stay aware of their surroundings to avoid surprising stray dogs; avoid carrying or eating food in the presence of monkeys; and avoid coming into contact with bats. Cavers in particular should be advised not to handle bats.

Pre-exposure vaccination

Pre-exposure vaccination should be offered to travellers at high risk of exposure to rabies. This

includes veterinarians, animal handlers and wildlife officers, and others living in, or travelling to, rabies endemic areas, especially for periods of more than 1 month. At risk groups include adults with high risk itineraries (as listed above), children living in or visiting rabies endemic areas, and individuals travelling to isolated regions where access to appropriate medical care, including effective, appropriate and timely PEP, is limited.^{13,22}

Vaccines

Vaccination against rabies is used for:

- pre-exposure vaccination, which aims to protect those at risk of being exposed to rabies, and
- PEP to prevent clinical rabies after exposure has occurred.¹³

The vaccines are the same, but the schedules for their delivery are different. Several safe, highly immunogenic cell culture vaccines exist¹⁴ and are recommended by the World Health Organization (WHO). Rabies vaccines available in Australia are:

- the human diploid cell rabies vaccine (HDCV), an inactivated virus vaccine. Each 1.0 mL dose contains at least 2.5 IU inactivated rabies virus, neomycin 100–150 µg, and up to 70 mg of human serum albumin⁴
- the purified chick embryo cell vaccine (PCECV) is also an inactivated virus vaccine. Each 1.0 mL dose contains at least 2.5 IU inactivated rabies virus, neomycin (trace amounts), chlortetracycline, amphotericin B, and traces of bovine gelatin and egg protein.

It is important to be aware that further vaccines are available overseas and returned travellers



Figure 1. Rabies endemic countries
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may present after receiving these. These include purified vero rabies virus (PVRV, Verorab) cultured on vero cells,^{17,23} rabies vaccine adsorbed (RVA), and a purified duck embryo vaccine (Lyssavac).²⁴ These vaccines are interchangeable.⁴ The schedule for pre-exposure vaccination is outlined in *Table 1*.

Both vaccines must be given via the deltoid region in adults and children 12 months or older. Children younger than 12 months may be given the vaccine via the anterolateral aspect of the thigh. Rabies vaccine should never be given via the gluteal region or administered to sites other than the deltoid (or anterolateral thigh) region, as this may result in lower neutralising antibody titres and vaccine failure.⁴ There is insufficient data to support schedules shorter than 21 days.⁴ Serological testing, done 2–3 weeks after the last vaccine dose to confirm seroconversion, is not routinely required but is necessary in people with impaired immunity.⁴

Contraindications and precautions

An individual with anaphylactic sensitivity to eggs or egg proteins should not be given PCECV (HDCV should be used instead).⁴ The vaccine is usually well tolerated. Minor adverse reactions, such as local pain, erythema, swelling and itching occur with variable frequency. Systemic reactions have been noted and include malaise, generalised aches and headaches.

Infants and pregnant women

Data in children aged less than 12 months are limited, but trials have demonstrated protective antibody titres in infants commencing a course of PVRV vaccine at 2 months of age, without severe adverse events.¹⁴ Babies who are not yet mobile are at lesser risk but may be exposed to bat bites.¹⁴

More than 200 cases of successful maternal vaccination during pregnancy without adverse fetal outcomes have been reported, and pre-exposure vaccination should be advised when there is substantial risk of maternal exposure to rabies.²⁵

Booster dosing

Booster dosing is not usually required for travellers. If risk of exposure persists, antibody titres are measured every 6 months in individuals at high risk (usually laboratory staff working with lyssaviruses), or every 2 years in others with ongoing risk of

Table 1. Rabies pre-exposure vaccination schedule⁴

Vaccine	Dose	Number of doses	Schedule (days)	Administration
HDCV	1 mL	3	0, 7, 28 (or 21)	Intramuscular (can be given subcutaneous)
PCECV	1 mL	3	0, 7, 28 (or 21)	Intramuscular

exposure. Booster doses are given if titres are <0.5 IU/mL,^{7,26} or every 2 years without serological testing.⁴ Serological testing gives an indication of adequate vaccination rather than protection, and has been expressed by the Advisory Committee on Immunization Practices as a serum dilution of 1:5.^{7,27} As this is the only means of testing vaccine efficacy, standardisation between laboratories across the world is essential.^{1,7,9} The gold standard assay to measure rabies virus neutralising antibodies is the rapid fluorescent focus inhibition test (RFFIT), although rabies specific antigen binding activity of antibodies can be measured through enzyme linked immunosorbent assays (ELISAs) or other methods.⁷

Intradermal pre-exposure vaccination?

The National Health and Medical Research Council (NHMRC) advises using the intramuscular (or subcutaneous, if using HDCV) route for administration of pre-exposure prophylaxis and rabies vaccines are not licensed for intradermal use in Australia.⁴ However, intradermal rabies vaccine may be given,²⁸ and results in protective immunologic response and substantial cost savings and greater acceptance by travellers,^{18,20,29,30} although antibody titres are lower and more transient with slower initial immune response. WHO supports the use of intradermal vaccination for rabies pre-exposure prophylaxis when vaccination is required at a lower cost.¹³ If the intradermal route is used, a regimen of 0.1 mL on days 0, 7 and 28 is appropriate. As administration of the vaccine must be by a practitioner with expertise in intradermal administration of vaccine, travellers should be referred to a travel clinic.⁴

Intradermal vaccination is contraindicated in individuals with impaired immunity and those taking the antimalarials chloroquine, mefloquine, or structurally related medications at the time of vaccination or within a month after vaccination. The vial must be discarded at the end of the vaccine

session, and antibody levels must be checked 2–3 weeks after completion of the vaccine course.

Postexposure prophylaxis

Prevention of rabies encephalitis involves preventing the virus from being taken up at a peripheral nerve synapse and entering the nerve by reducing viral load at the exposure site.^{3,7} It includes:

- thorough wound cleansing and disinfection
- passive immunisation by instillation of rabies neutralising antibodies into the wound, and
- stimulation of an active immune response with rabies vaccine.³

Postexposure prophylaxis is virtually 100% effective when given correctly.⁷ Pregnancy, infancy, older age and concurrent illness are not contraindications for rabies PEP in the event of exposure.²¹

Recommended PEP depends on the category of risk of the exposure to rabies (*Table 2*). The PEP regimen for both rabies and ABL is summarised in *Table 3*.

Australian bat lyssavirus PEP

Postexposure prophylaxis for ABL should be considered whenever a bite, scratch or mucous membrane exposure to saliva from any Australian bat has occurred, regardless of extent of injury, time lapsed since exposure, bat species and bat health status. If possible, the bat should be kept for official testing; human rabies immunoglobulin (HRIG) and vaccine (after appropriate wound management) can be withheld if a result can be obtained within 48 hours, otherwise full PEP is indicated. If the bat is found to be negative after 48 hours, PEP can be discontinued. Exposure to bat blood, urine or faeces, or to a bat that has been dead for >4 hours, is not an indication for PEP.⁴

Wound management

All wounds must be thoroughly cleaned with copious soap or detergent and water, followed by

Table 2. Possible exposures to rabies and post-exposure treatment¹³

Category	Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for testing	Type of exposure	Recommended postexposure prophylaxis
I	<ul style="list-style-type: none"> • Touching or feeding of animals • Licks on intact skin 	None	None, if reliable case history available
II	<ul style="list-style-type: none"> • Nibbling if uncovered skin • Minor scratches or abrasions without bleeding 	Minor	Administer vaccine immediately. Stop treatment if animal remains healthy throughout a 10 day observation period or is proved to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques
III	<ul style="list-style-type: none"> • Single or multiple transdermal bites, scratches or licks on broken skin • Contamination of mucous membranes with saliva (licks) • Exposure to bats 	Severe	Administer rabies immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout a 10 day observation period or is proved to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques

Table 3. Summary of Australian bat lyssavirus and rabies postexposure prophylaxis for nonimmune individuals⁴

Treatment	Immediate (day 0)	Follow up
Local treatment	Thorough wound cleansing and management	
Rabies vaccine	1.0 mL	1.0 mL on days 3, 7, 14, 28–30
HRIG (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

povidone iodine. Suturing should be delayed where possible. If suturing is unavoidable, the wound should be infiltrated with rabies immune globulin (RIG) and suturing delayed for at least several hours.^{3,4,13} Tetanus vaccination and antibiotics should be given where indicated.

Passive immunisation

All category III exposures (and category II exposures in immunosuppressed travellers) should receive rabies immune globulin (RIG). In Australia, as in most developed countries, HRIG is available.⁴ However, a global shortage of HRIG means that many developing countries (including Thailand) use equine rabies immunoglobulin (ERIG) instead; this is preferable to not administering RIG at all,³ and the incidence of adverse reactions, mainly serum sickness (which commonly occurs a week later), is low (0.8–6.0%).^{3,31} A recent study suggests that the mandatory skin test recommended before ERIG administration⁵ does not necessarily predict serum sickness.³¹ Higher adverse event rates (including anaphylaxis) occur after administration of unpurified antirabies sera where HRIG or ERIG are not available.³

Administration of immunisation

As much as possible of the calculated dose of 20 IU/kg HRIG is infiltrated into and around the wound site. If wounds are extensive, RIG should be diluted with normal saline to extend the number of wounds that can be injected.³ Any remaining RIG is to be injected intramuscularly (IM) into the deltoid muscle on the opposite side of the wound (the anterior thigh is an alternative site). The site must be distant from the site of vaccine administration. Rabies immune globulin should be given even when there is a significant delay to the possible exposure, but it should not be given more than 7 days after the start of the postexposure vaccine series³ if an appropriate modern rabies vaccine has been used.¹³

Active immunisation

The NHMRC recommends the Essen regimen: five doses of 1.0 mL of rabies vaccine IM on days 0, 3, 7, 14, and 28 or 30 in the deltoid muscle (or anterolateral thigh in infants aged <12 months).^{4,13} The alternative Zagreb regimen involves two doses on day 0 (one in the right deltoid and one in the left), and one dose on each of days 7 and 21. Travellers may have received this regimen

overseas. Less expensive intradermal regimens also exist and are in use overseas.

If a traveller has received a cell culture derived vaccine while overseas, the standard PEP regimen should be continued and HRIG should be given as soon as possible if it was not administered and the person presents within 7 days of PEP commencement. Postexposure prophylaxis may be ceased if the animal is definitely found to be negative for rabies after testing in a reputable laboratory, or it can be ascertained with absolute reliability that the animal has remained well for more than 10 days.⁴

Nerve tissue vaccines

A number of countries have not switched over to WHO recommended cell culture vaccines, including Pakistan, Burma, Bangladesh, Peru and Argentina.⁸ In many other countries such as India and Vietnam, modern cell culture vaccines are available in the private health sector, while nerve tissue vaccines tend to be the most accessible vaccines in rural areas and government health facilities. This is also the case in many Andean and Central American countries, and in Africa. The original nerve tissue vaccines, first used by Pasteur, are prepared from animal brain tissue and may require 7–21 daily injections of up to 5 mL, usually subcutaneously, (sometimes intradermal, as in the suckling mouse vaccine used in Vietnam) and additional boosters, totaling a volume of up to 40 mL per course. They are not recommended by WHO and have a 0.1–5.0 per 1000 rate of serious neurological complications, including Guillain-Barre syndrome, which can lead to death or permanent disability in up to a quarter

of these patients.⁵ Travellers need to be aware of these vaccines and should not accept them, but should travel to a country where cell culture vaccines and appropriate immune globulin are available.³

PEP in previously vaccinated travellers

Previously vaccinated travellers can be treated with a modified PEP regimen. After appropriate wound management, two 1.0 mL IM booster doses should be given on days 0 and 3. Rabies immunoglobulin is not necessary.^{4,13} If documentation of a full course of rabies pre-exposure vaccine is not available, standard PEP (HRIG and five doses of rabies vaccine) should be given.⁴

Future developments in rabies control

As rabies tends to be a problem in the developing world, research into improved control has been slow. Recent research has focused on improving control of the disease (such as by vaccination of dogs) and reducing cost and complexity of vaccines and immunoglobulin products. However, such strategies have been prone to failure in developing countries and new vaccines are needed for large scale pre-exposure vaccination of children in resource poor countries as well as for PEP.^{1,9} These should preferably be cheap, with single (or reduced) dosing, low in side effects and rapidly protective in the case of PEP, ideally requiring less or no RIG.^{1,9} Numerous vaccine prototypes are in preclinical development,¹ as well as a human monoclonal antibody cocktail (CL184) for use in human rabies PEP instead of RIG.³² In the meantime, a preliminary study has suggested the possibility of developing a 1 week or single visit intradermal pre-exposure vaccine schedule designed to provide immunity for at least 12 months.³³ Recent studies on patients with HIV and those on renal dialysis using intradermal rabies vaccination suggest that the intradermal route may be considered appropriate for PEP in immunocompromised individuals.^{34,35}

Summary

All travellers require education regarding rabies prevention if travelling to a rabies endemic area, including a discussion regarding avoidance of high risk activities. Those at high risk of exposure should be offered pre-exposure vaccination. Modern cell

culture vaccines are well tolerated, although cost and time taken to complete the course can be of concern to travellers. Postexposure prophylaxis should always be commenced where indicated, as no contraindications exist. Products and vaccine regimens used overseas may differ, and an awareness of these is helpful for the traveller in order to make informed decisions about treatment. Further research is needed into rabies control as well as pre-exposure vaccination and PEP to increase accessibility and decrease cost and complexity.

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