Rabies: an evidence-based approach to management

Blumberg L, M Med (Micro), FFTM (Glasgow)
Weyer J, PhD
Frean J, M Med (Micro), FFTM (Glasgow), FACTM
National Institute for Communicable Diseases (NICD), National Health Laboratory Service, Johannesburg
Ogunbanjo GA, FCFP(SA), M Fam Med, FACRRM, FACTM
Dept. of Family Medicine & PHC, University of Limpopo (Medunsa Campus), Pretoria

Correspondence to: Dr Lucille Blumberg, e-mail: lucilleb@nicd.ac.za

Abstract

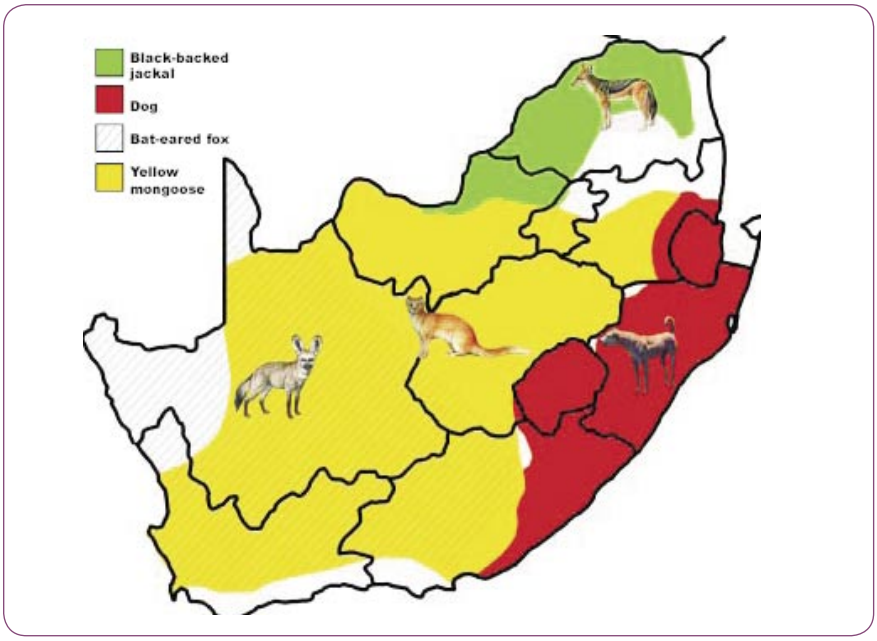
Human rabies in South Africa is largely due to infection with the classical rabies virus (genotype 1), with the yellow mongoose the commonest vector except in KwaZulu-Natal, Eastern Cape, Mpumalanga and now Limpopo provinces where the dog is predominantly responsible for most bites. Rabies is always fatal in humans but can be prevented by timeous administration of post exposure prophylaxis(PEP). This article discusses an evidence-based approach to rabies management in South Africa.

SA Fam Pract 2007;49(5): 35-41

Introduction:
Animal rabies is endemic in South Africa and causes 10 to 30 laboratory-confirmed human deaths annually. It is likely that the number of actual human cases is significantly higher with patients either dying in the community or the disease unrecognized by health professionals as a possible cause of any encephalitis-type illness. Human rabies in South Africa is largely due to infection with the classical rabies virus (genotype 1) with the Duvenhage virus (genotype 4) to date identified in only two human infections, both of which followed bat exposures.[1,2] Both wild and domestic animals are important reservoirs, with dogs being the major vector for human disease. Major vectors responsible for transmission vary geographically in South Africa (Figure 1).

Rabies virus gains entry into the human host by the introduction of virus-containing saliva into a bite wound, or by saliva contamination of mucous membranes of the mouth, eyes, nasal passages and broken skin. After a variable period of local virus proliferation in non-neural tissue, it gains entry into the peripheral nerves and is transported along afferent axons to the central nervous system (CNS) leading to an almost uniformly fatal encephalitis. Rabies has the highest fatality of any human infection, but appropriate and timeous post exposure preventative treatment is highly effective in preventing rabies disease.[2]

Figure 1: Rabies is endemic to South Africa. The major vectors of the disease involved are indicated on the diagram.



(Reprinted with permission from Rabies: Guide to Medical, Veterinary and Allied Professions. Department of Agriculture, South Africa)

The following three scenarios related to actual or potential animal bite exposures are presented for your consideration.

CASE 1
A 4-year-old child on a farm in KwaZulu-Natal was bitten on the face by the family dog and sustained a 1cm laceration on the cheek. The attack was unprovoked; the dog was unusually aggressive, died 2 days later and was buried immediately. The vaccination history of the dog was unclear. **How would you manage this child?**

CASE 2
A 10-year-old child presented with pain in the arm, fever and headache followed by an illness characterized by periods of lucidity, hallucinations and confusion. There was a history of a dog bite two months ago on the arm. The patient received tetanus vaccination and antibiotic at a local clinic after the bite incident. **What are the differential diagnoses and indicate the laboratory investigations you would do?**

CASE 3

A newly-qualified game guide is going to work in Zambia, doing surveillance work on zoonotic diseases. He asks your advice about personal prevention of rabies. **What would be your response to his request?**

CASE 1

This incident occurred in a rabies-endemic area and was unprovoked. Prevention of rabies disease in this child is mandatory. In addition, the bite is on the face and this could be associated with a shorter incubation period and even greater risk of disease. Although there is no confirmation of rabies in the animal, the absence of vaccination records for the dog and its behaviour should raise concerns about the risk of rabies. Since rabies is always fatal in humans, post-exposure prophylaxis (PEP) or post-exposure treatment (PET) may be life-saving and should be instituted immediately. The principles of PEP or PET are: remove free virus from tissues by washing; neutralize virus by passive immunity and induce a rabies virus-specific immune response in the exposed individual before rabies virus can replicate in the central nervous system (CNS).

PET should always be given if there is the slightest suspicion that the animal may be rabid. It is crucial to consider the following:

1. **Species of animal involved:** important animal species associated with rabies in Africa are dogs, cats, cattle, mongooses, foxes, and jackals (no transmission from mice, rats or vervet monkeys and two cases related to baboons in South Africa. Rabies-associated viruses are associated with bats in South Africa.
2. **Behaviour of the animal:** provoked or unprovoked attacks; rabid animals are usually aggressive but rabid wild animals may on occasion appear "tame". Frequently cattle and goats appear to choke due to an apparent 'bone in the throat'.
3. **Category of exposure:** PET must be administered in category 2 and 3 exposures (Table I).
   - Under no circumstance should PET be delayed pending confirmatory laboratory tests in the animal.
   - There is no blood test in the patient to confirm or exclude rabies transmission from the animal and the decision to give PET is based entirely on the perceived risk of rabies.
   - PET should not be withheld even if there has been a delay in the person presenting to the health facility, although efficacy may be suboptimal.
   - Vaccination history of the animal may be unreliable and animals that have been vaccinated before 3 months of age and those who have not received boosters may not be protected from rabies.

Management of the patient exposed to a potentially rabid animal [3,4,5]

a. General wound management is critical in all patients: *
- The bite site should be well flushed with soap and water or water alone for at least 5 minutes before applying disinfectant e.g. 70% alcohol or iodine solution
- It is advisable to avoid suturing of the bite wound and the use of local anaesthetics

b. Further specific management depends on category of rabies exposure (Table I)
- Vaccine course in category 2 and 3 exposures
- Addition of rabies immunoglobulin in category 3 exposures is critical

c. Role of human rabies vaccine ϕ

Human rabies vaccines available in South Africa are cell-derived, either produced on VERO cells (Verorab®) or chick embryo cells (Rabipor®). Cell derived-vaccines are of high efficacy and safe with few adverse reactions. The vaccines must be administered intramuscularly into the deltoid, or anterolateral thigh in children, but NEVER into the buttocks as the immune response may be suboptimal. The dosage varies according to manufacturers, but it is usually 0.5 – 1ml. The full course must be administered to affect an adequate and prolonged immune response.

A vaccine course comprises of 5 vaccines administered on days **0, 3, 7, 14,** and **28,** with day **0** being the day of the first vaccine administration. The vaccine is ideally given as soon as possible after exposure, and should still be given even if a patient presents some time after the exposure. The paediatric and adult dose is the same and adverse events are uncommon. Local reactions include pain, erythema, swelling or itching at the injection site. Systemic reactions include fever, arthralgia, arthritis, angioedema, nausea, vomiting and malaise.

d. Role of Rabies Immune Globulin (RIG) #

Anti-rabies immunoglobulin (Rabigam® National Bioproducts Institute, Pinetown, KZN) is prepared by fractionation of pooled serum from immunized human donors. RIG is indicated for all category 3 exposures. The method of administration is to infiltrate as much as possible of the

Table I: Categories of animal exposure

Risk Category	Type of exposure	Action
1	Touching or feeding animal. Licking intact skin.	Nil if reliable history
2	Nibbling uncovered skin. Superficial scratch without bleeding.	• Wound treatment* • Give rabies vaccine ϕ • Do not give anti-rabies immunoglobulin • Stop vaccination if animal negative for rabies (laboratory tests) or remains well after 10 days observation (dog or cat)
3	Bites or scratches penetrating skin & drawing blood. Licking of mucous membranes or broken skin.	• Wound treatment* • Give rabies vaccine ϕ • **Give anti-rabies immuno globulin #** • Give anti-tetanus vaccine and antibiotic • Stop vaccination if animal negative for rabies (laboratory tests) or remains well after 10 days observation (dog or cat)

RIG into the wound at a dosage of 20 IU/kg (Rabigam - each 2 ml ampoule contains 300 IU). **Local aneasthetic should not be used as it may interfere with the local action of the RIG.** The remaining RIG is given in the opposite deltoid to that used for the vaccine. If there are multiple wounds, the RIG can be diluted with saline by 2 or 3 times so that all wounds are adequately infiltrated.
RIG should be given as soon as possible after exposure, but may be administered up to 7 days after the first vaccine is given. It is important not to exceed the maximum dose as antibody response to the vaccine is inhibited. If RIG is unavailable, active immunization with vaccine should not be delayed. In addition, RIG should not be given to the patient if there is a history of pre- or post-exposure prophylaxis. Adverse events are generally uncommon and are the same as for the vaccine.

e. Special circumstances

- **Bat exposures:** PET provides variable protection against rabies-related viruses. The categories of exposure (Table I) do not apply to bats, as transmission can occur with very minor or even inapparent contact. Any close contact with bats is an indication for PET and should be managed as a category 3 exposure.
- **Immunocompromised persons:** RIG plus vaccine should be used for category 2 as well as category 3 exposures because of decreased efficacy of vaccine.
- **Pregnant women;** Pregnancy is not a contra-indication for the vaccine or RIG, if there has been a significant rabies exposure.

CASE 2

Rabies should be suspected in all severe, acute neurological disease of suspected viral origin especially if the disease progresses to coma and death.[6] The typical clinical presentation of rabies is summarised as follows:

- Incubation period 2-8 weeks (range: 5 days to 1 year).
- Onset may begin with fever, headache, nausea, diarrhoea, irritability.
- One third may report paraesthesia or itching at site of bite.
- Acute neurologic phase – agitation, mania, hyperactivity, and hallucinations interspersed with lucid periods.
- Rabies may present as a predominantly paralytic disease (Table II).
- Seizures may be precipitated by auditory or tactile stimuli.
- Hydrophobia or aerophobia may occur; hypersalivation is common.
- Death is usually due to cardio-respiratory failure.

Reliable case histories provide valuable information that may guide the medical health professional to include or exclude rabies as a likely cause of illness. Important points to address with suspected rabies cases will include the geographical locality of the possible exposure event, where cases from endemic areas should be considered of higher risk. Details, including ownership, vaccination status and behavioral characteristics of the dog (or other animal) involved in the possible exposure are particularly useful. In all patients with a history of dog bite and where the dog cannot be accounted for (i.e. a stray animal or no vaccine certificate available),

Table II: Differential diagnosis for patients presenting with 'rabies-like' illness.

Etiology	Diagnosis	Clinical presentation	Considerations
Non-infectious	Delirium tremens	Confusion, agitation, hallucinations, uncontrollable tremors of the extremities	Only in patients with history of excessive alcohol abuse, followed by abstinence
	Drug reaction	Tremors, restlessness, agitation, hyper salivation	Substance abuse, neuroleptic drugs, organophosphates
	Strychnine poisoning	Convulsions, agitation, restlessness, spasms	Sudden onset (within 60 minutes of ingesting the poison)
	Snake bite poisoning (from elapid snakes)	Uncontrolled salivation (dribbling from mouth, due to throat paralysis)	A swollen bite wound should be present on the body; ptosis often present
Infectious	Tetanus	Convulsions on sudden stimuli, trismus, difficulty swallowing	Vaccination history of the patient must be considered; Patient will present with clear consciousness and no signs of encephalitis; Rabies patients usually don't have sustained rigidity of the axial muscles (i.e. jaw) as with tetanus
	Bacterial meningitis	High fever, headache, confusion, sleepiness, irritability, nausea, seizures	Abnormal CSF
	Viral encephalitis	General encephalitic picture	No clear behavioral changes, no lucid periods and no typical spasms; Midline structure involvement on magnetic resonance imaging (MRI); Causative agents include herpes simplex virus and different arboviruses; Travel history is an important consideration for possible arbovirus cases
	Cerebritis, encephalitis	Impaired consciousness, generalized convulsions, coma	Malaria, trypanosomiasis: history of travel and exposure, confirmatory blood tests
	Acute flaccid paralysis/polio	Weakness: flaccid paralysis	Patients have clear consciousness

rabies must be considered a probable diagnosis. A number of diagnoses may be considered when the case history indicates that rabies is not likely (Table II).

Clinical signs may be obscure and laboratory testing is important to confirm a suspected diagnosis, since every rabies-associated death should be regarded as a health system failure. It is critical that human cases of rabies are confirmed and notified so that the problem of rabies is recognized in the area and public health programmes strengthened. Laboratory confirmation of rabies in humans is however hampered by the limited availability of laboratory tests, delays in diagnosis and the requirement for invasive diagnostic procedures postmortem. Although ante-mortem testing is not considered the 'gold standard' and is not 100% sensitive, it should be definitely attempted.

The rapid and accurate diagnosis of rabies *intravitam* is essential to ensure appropriate medical management of the patient, which is particularly important when the disease is caused by a treatable agent and not rabies virus.

Early indication of a case may also aid in timely public health intervention for other possible contacts and guide management of medical staff and the patient's relatives. Routine examination of the CSF is generally not helpful, and is typically normal. Pleocytosis may be found after 7 days of illness.[7] Magnetic resonance imaging (MRI) may provide some insights, but computed tomography (CT) is normal and electroencephalography (EEG) usually shows diffuse slow wave activity.[8] Several specialized laboratory tests are available for confirmation of rabies, ante- and postmortem (Table III). The most useful antemortem test is the reverse transcription polymerase chain reaction (RT-PCR), which detects the viral genome and can be applied to saliva, cerebrospinal fluid or nuchal biopsy specimens.

Table III: Summary of laboratory tests for confirmation of rabies ante- or postmortem.

Specimen	Laboratory test	Sensitivity/ interpetation of results	Comments
Saliva	RT-PCR	Sensitive, but negative result does not exclude rabies virus infection. Sequential specimens should be submitted for testing	Saliva, not sputum should be used
	Virus isolation	Cell culture or laboratory animal isolation of virus	Delay in results and not all strains may be adaptable to cell culture
CSF	RT-PCR	Negative result does not exclude rabies virus infection	Saliva usually more sensitive specimen Delay in results and not all strains may be adaptable to cell culture Antibodies in the CSF are regarded as an indication of infection (and not vaccination). May be present in cases who have received rabies vaccine
	Virus Isolation	Cell culture or laboratory animal isolation of virus	
	FAT	A negative result does not exclude rabies virus infection, and antibodies may only be detected late during disease (typically after 5 days of infection)	
Serum	FAT	As for CSF	Detect antibody after vaccination or response to infection in unvaccinated patients
Brain	FAT	Sensitivity approaches 100 % in experienced laboratories	Gold standard for rabies postmortem diagnosis
	RT-PCR	Sensitive, and may be especially useful for specimens fixed in formalin	
	Virus isolation	Cell culture or laboratory animal isolation of virus	

Tests not routinely available in testing laboratories are not included.

Saliva is however the preferred specimen for testing in most laboratories. Fluorescent antibody test (FAT) on nuchal biopsies is useful but requires specialized equipment and may not be available in all testing laboratories. FAT on corneal impressions is also not preferred. The benchmark for postmortem rabies diagnosis, the fluorescent antibody test (FAT) detects viral antigen in brain smears.[9] The test is 100% sensitive when performed in experienced laboratories. When an autopsy is not agreed to by the patient's relatives, the collection of a brain biopsy through the superior orbital fissure is suggested.[10] Postmortem diagnosis through histology may also be useful but is less sensitive than the aforementioned tests.[11] Microscopic investigation of stained sections of hippocampus, brain stem and cerebellum revealing oval-shaped inclusion bodies known as **Negri bodies** are considered a positive indication of rabies virus infection. Important points regarding the laboratory diagnosis of rabies virus infection which are often a source of uncertainty are as follows:

- **There is no blood test to confirm rabies virus infection (or exposure).** Rabies virus is not viraemic and cannot be detected in blood specimens. Serum antibodies as a response to infection are produced late during disease, and are not reliable for diagnosis. Detection of serum antibodies in unvaccinated patients may however be diagnostic, but usually only appears late during the disease.
- **Sequential saliva specimens should be submitted for laboratory testing in clinically suspected cases (intra vitam).** Saliva specimens are the preferred specimens for laboratory

diagnosis in most laboratories, but importantly, a negative result does not exclude rabies virus infection (especially in early disease) and testing sequential specimens is important.

- Postmortem diagnosis of suspected rabies cases does not only provide closure for the patient's relatives but also provides important information to authorities to motivate better control strategies in animals or distribution of prophylaxis. Brain (complete in two halves, or pieces or trucut needle biopsies of preferably the cerebellum and brainstem, in 50% glycerol buffered saline (in screw cap containers) should be sent to reach the testing laboratory as soon as possible after collection.

Rabies has 100% mortality and there is no specific management for patients. Sedation of the patient[12], supportive care should be considered, and although there has never been a person-to-person transmission other than through rare transplantation cases, infection control procedures for heath care workers should be instituted by the use of personal protective equipment. Rabies immunoglobulin and vaccine play no role once clinical disease is apparent. To date there has been only one human rabies disease survivor without any PET, a young girl who developed rabies following on a bat exposure, and who survived following on induced coma, critical care support and the use of antiviral agents.[12]

CASE 3

People with increased occupational risk of exposure to infection, such as veterinary staff, wildlife handlers, laboratory personnel working with rabies virus or animal welfare staff, should receive pre-exposure prophylaxis by administration of three doses of vaccine into the deltoid muscle on days **0, 7** and **28**.

Persons who have received pre-exposure vaccination must be given two booster doses of vaccine if there is exposure to a suspected rabid animal. These are given on days 0 and 3. Rabies immune globulin should be omitted post exposure since it may depress the rapid boosting of antibodies. It is not clear how often boosters should be given in this group of people with ongoing potential exposure; some authorities recommend boosters every 3-5 years. Measurement of serum antibody levels by neutralization testing may guide the process. A recent study demonstrated that even after 18 years, a single vaccine booster will result in a rapid and significant increase in antibody titers.

Table IV: Important health promotion messages for the community

1. **Rabies kills; Have your dog or cat vaccinated against rabies every year**
2. **Do not touch wild or stray animals**
3. **It is critical to educate children to report any animal bite or scratch even, even if from their own or neighbour's pet (90% of rabies cases are in children)**
4. **All animal bites and scratches must be washed thoroughly with water for at least 5 minutes before going to the clinic/hospital**
5. **All people bitten by animal must go to the clinic/hospital for preventative treatment**

Rabies and the traveler: Rabies is an important disease for the traveling community. Canine and feline rabies are endemic in the developing countries of Asia, Africa and South America. This poses a particular threat in the backpacking or adventure category. Pre-exposure rabies vaccination, as above, should be considered. Pre-exposure immunization obviates the need for post-exposure rabies immunoglobulin, a commodity which is often unavailable in many countries.

Conclusions:

Human rabies in South Africa is largely due to infection with the classical rabies virus (genotype 1), with the yellow mongoose the commonest vector except in KwaZulu-Natal, Eastern Cape, Mpumalanga and now Limpopo provinces where the dog is predominantly responsible for most bites. Rabies is always fatal in humans and post-exposure prophylaxis (PEP) or post-exposure treatment (PET) is appropriate immediately after a bite. PEP follows a schedule of 3 doses of vaccine in the deltoid muscle on days 0, 7 and 28, and patients who had pre-exposure vaccination receive only two vaccine booster doses on days 0 and 3, with new exposure to a suspected rabid animal. Finally, there is no blood test to confirm rabies virus infection (or exposure), hence it is unnecessary to request such test when confronted with a patient possibly exposed to rabies. Table IV lists important health promotion messages for the community.

Acknowledgement:

Department of Agriculture, South Africa for the permission to reprint the major vectors of the disease involved as indicated on the diagram (Figure 1).

References:

1. Rabies Guide for the Medical, Veterinary and Allied Professions, South African Department of Agriculture, revised 2007.
2. Paweska JT, Blumberg LH, Liebenberg C, Hewlett RH, Grobbelaar AA, Leman PA, Croft JE, Nel LH, Nutt L, Swanepoel R. Fatal human infection with rabies-related Duvenhage virus, South Africa. Emerging Infectious Diseases 2006; **12** (12): 1965-1967
3. Jackson AC, Warrell MJ, Rupprecht CE, Ertl HC, Dietzschold B, O'Reilly M, Leach RP, Fu ZF, Wunner WH, Bleck TP, Wilde H. Management of rabies in humans. Clinical Infectious Diseases 2003; 36: 60-63
4. Mallewa M, Fooks AR, Banda D, Chikungwa P, Mankhambo L, Molyneux E, Molyneux ME, Solomon T. Rabies encephalitis in malaria-endemic area, Malawi, Africa. EID 2007; 13 (1): 136-139.
5. WHO Expert Consultation on Rabies, First Report. WHO Technical Report Series 931 2005; WHO, Geneva.
6. Hemachuda T, Laothamatas J, Rupprecht CE. Human rabies: a disease of complex neuropathogenetic mechanisms and a diagnostic challenge. Lancet Neurology 2002; **1**: 101-109.
7. Jackson AC. Rabies. Can J Neurol Sci 2000; **27**: 278-82.
8. Laothamatas J, Hemachuda T, Mitrabhakdi E, Wannkrairot S, Tulayadaechanont S. MR imaging in human rabies. Am J Neuroradiol 2002; **23**: 632-634.
9. Dean DJ, Abelseth MK, Atanasiu P. The fluorescent antibody test. In: Meslin F-X, Kaplan MM, Koprowski H, eds. Laboratory techniques in rabies. 4th Edition. Geneva: World Health Organization, 1996: 88-95
10. Tong T, Leun KM, Lee KC, Lam AWS. Trucut needle biopsy through superior orbital fissure for diagnosis of rabies. The Lancet 1999; **354**: 2137-2138.
11. Jogai S, Radotra BD, Banerjee AK. Immunohistochemical study of human rabies. Neuropathology 2000; **20**: 197-203.
12. Willoughby RE, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ, Chusid MJ, Rupprecht CE. Survival after treatment of rabies with induction of coma. N Engl J Med 352; **24**: 2508-2514