National Guidelines for the Prevention of Rabies in Humans, South Africa

National Department of Health
National Institute for Communicable Diseases
September 2021

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Health
REPUBLIC OF SOUTH AFRICA

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

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Contents

I. PREFACE

Rabies is endemic in South Africa (SA), with an average of 10 laboratory-confirmed cases of human rabies confirmed annually. Rabies is a fatal but preventable infection and a human case of rabies is a failure of the health care system.

Rabies in SA is addressed through a 'One Health Approach' by the National Department of Health (NDoH), Department of Agriculture, Land Reform and Rural Development (DALRRD), National Institute for Communicable Diseases (NICD), as well as many other stakeholders. It is through collaboration, coordination and communication that improved health outcomes for both humans and animals are possible. These guidelines represent a multi-sectoral effort to improve the management of animal bites/suspected rabies exposures in humans thereby preventing human rabies.

II. ACKNOWLEDGEMENTS

The NDoH continuously emphasises the importance of multidisciplinary and multisectoral collaboration, in particular on policy development and implementation of strategies for the control of communicable diseases. The 'National Guidelines for the Prevention of Rabies in Humans, South Africa' document has therefore been developed by the NDoH in collaboration with various stakeholders who collectively form the *Rabies Working Group*. This working group represents the following organisations:

- National Department of Health
- Department of Agriculture, Land Reform and Rural Development
- National Institute for Communicable Diseases
- Amayeza Info Services
- University of Pretoria

The NDoH would like to thank all the contributing members in the group and would also like to thank provincial health and veterinary services, academic institutions and researchers for their valuable contributions. We are confident that all healthcare providers, in all health sectors, will find this document useful as they strive to improve the management of animal bites and the prevention of human rabies in our country.

Special mention must also be made of the former Rabies Advisory Group (2002), which laid the foundation for the first edition in writing, 'Rabies, Guide for the medical, veterinary and allied professions'. Gratitude is also extended to all the reviewers and contributors of the second edition (2010).

III. ABBREVIATIONS

DALRRD	Department of Agriculture, Land Reform and Rural Development
ERIG	Equine-derived rabies immunoglobulin
HRIG	Human-derived rabies immunoglobulin
ID	Intradermal
IM	Intramuscular
IU	International units
Kg	Kilogramme
mL	Millilitre
NICD	National Institute for Communicable Diseases, a division of the National Health Laboratory Service
NDoH	National Department of Health
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
RIG	Rabies immunoglobulin
SA	South Africa
WHO	World Health Organization

IV. DISCLAIMER

This material is intended for use by healthcare professionals. It has been compiled from information currently available and although the greatest care has been taken; the NDoH, NICD and the Rabies Working Group do not take responsibility for errors or omissions. In particular, it should be noted that the epidemiology and epizootiology of rabies is dynamic and may change over time – when considering risk assessment for possible rabies exposure, consult current data for the occurrence of rabies in animals.

The use of trade names in this document does not constitute endorsement of any specific product, but serves to inform healthcare professionals of registered and/or available products for the prevention of rabies in humans in South Africa and guide on the appropriate use of these products.

Readers are directed to the reference articles for further information and should exercise their own professional judgment in confirming and interpreting the findings of the publication. These guidelines were issued in 2021 and should replace all previous guidelines on the prevention of rabies in humans in SA.

1. INTRODUCTION

Rabies is an important but neglected zoonosis that can affect all mammalian species, including humans. The lyssavirus genus is diverse and consists of several viral species that can all cause the disease rabies. Rabies *lyssavirus* is however responsible for the majority of cases. This virus has a predilection for neural tissue and, as such, spreads via peripheral nerves to the central nervous system causing fatal encephalitis. Rabies can however be successfully prevented through the application of post-exposure prophylaxis (PEP), which includes thorough wound washing and the administration of the rabies vaccine with or without rabies immunoglobulin (RIG). In April 2018, the WHO published its revised position on rabies vaccines and rabies immunoglobulins[1]. This document follows the guidance and science shared in that paper and summarises the current recommended rabies PrEP and PEP regimens in SA as of February 2021.

There is limited systematic surveillance of human rabies in most affected countries. The WHO reports that up to 59 000 cases of human rabies occur annually. These cases are largely reported from developing countries in Africa and Asia and are predominantly related to exposure to rabid dogs as a result of poor control of canine rabies. Approximately 10 cases of human rabies are reported annually in SA by laboratory-informed surveillance established at the NICD in 1983. Most of these cases occur after exposure to rabid dogs.

The information presented in sections 2 and 3 provides a background to the guidelines for the management of potential exposures to rabies in humans in SA, and does not replace requirements of national regulations and/or guidelines for the diagnosis and surveillance of human or animal rabies in SA[2].

2. RABIES IN ANIMALS

2.1 Epidemiology of animal rabies in SA

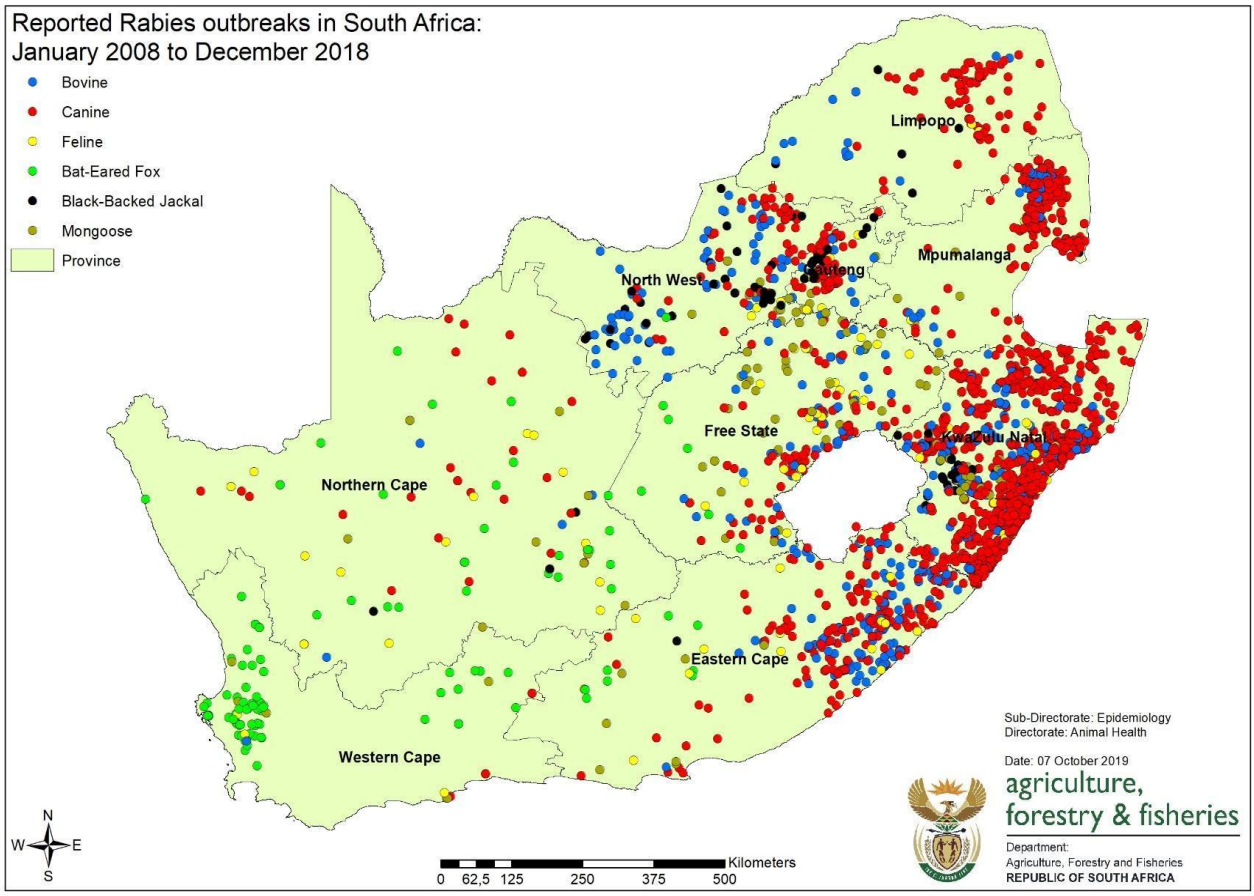


Figure 1. Geographical distribution of laboratory-confirmed cases of animal rabies in SA, 2008-2018. The canine cases include cases reported in domestic dogs (Map courtesy of DALRRD).

Knowledge of the distribution of cases of animal rabies is important when considering the risk of exposure to rabies in animal bite cases. The distribution of animal rabies cases in SA between 2008 and 2018 is shown in Figure 1. Rabies is reported from wildlife and domestic animal hosts in all provinces of the country. Rabies is maintained in cycles involving domestic dog (in red), black-backed jackal (in black), mongoose (in olive green) and bat-eared fox (in bright green). Cases in domestic dogs have mostly been reported from areas in the eastern half of SA. Cycles of rabies in black-backed jackals largely overlap with areas where rabies is reported in domestic dogs, and it is expected that these cycles may be interlinked or interdependent in some areas. Rabies in mongooses have been found across the central plateau of the country, while rabies in bat-eared foxes have been reported mostly from areas of the Western Cape Province, from the Northern Cape and western Free State, Eastern Cape and North West provinces. Rabid animals may however appear anywhere in the country due to translocation of animals.

A list of the animal species with confirmed rabies from 2013-2018 in SA is provided in Table 1.

Table 1. List of laboratory confirmed rabies cases in animal species in SA, January 2013 – June 2018 (data from DALRRD as available on 7 June 2018).

SPECIES	NUMBER OF CONFIRMED CASES
Wildlife species	
Aardwolf (*Proteles cristata*)	31
African civet (*Civettictis* civet)	1
African wild cat (*Felis silvestris lybica*)	1
Bat-eared fox (*Otocyon* megalotis)	57
Black-backed jackal (*Canis mesomelas*)	15
Cape fox (*Vulpes chama*)	4
Cape clawless otter (Aonyx capensis)	1
Cape ground squirrel (*Xerus inauris*)	2
Caracal (*Caracal caracal*)	3
Common duiker (*Sylvicapra* grimmia)	4
Herpestid, unidentified species	15
Honey badger (*Mellivora capensis*)	9
Large grey mongoose (*Herpestes ichneumon*)	8
Rock hyrax ("dassie", *Procavia capensis*)	1
Selous' mongoose (*Paracynictis* selousi)	1
Serval (*Leptailurus serval*)	3
Side-striped jackal (*Canis adustus*)	5
Slender mongoose (*Galerella sanguine*)	7
Small grey mongoose (*Galerella pulverulenta*)	8
Small-spotted cat (Felis nigripes)	1
Small-spotted genet (*Genetta genetta*)	2
Spotted hyena (*Crocuta crocuta*)	1
Striped pole cat (*Ictonyx striatus*)	7
Suricates (species not reported)	7
Water mongoose (*Atilax* paludinosus)	16
White-tailed mongoose (*Ichneumia albicauda*)	3
Wild dog (*Lycaon pictus*)	1
Yellow mongoose (*Cynictis penicillata*)	49
Domesticated species	
Bovine (domestic cattle)	370
Goat (*Capra aegagrus hircus*)	71
Domestic cat (*Felis catus)*	67
Domestic dog (*Canis lupus familiaris*)	1 089
Equine (domestic horses)	19
Ovine (sheep)	26
Suis (domestic pigs or *Sus domesticus*)	1

2.2 Clinical presentation in animals

Understanding the clinical presentation of rabies in animals may aid to assess the risk of rabies virus transmission in animal bite cases. Apart from behavioural changes, there are no definitive clinical signs of rabies specific to a species. Although certain clinical signs are reported more frequently than others, even the most experienced veterinary professional may make an incorrect diagnosis when presented with an atypical case. The clinical presentation of rabies overlaps with many other diseases, but neurological signs are dominant due to the virus targeting the central nervous system. The consequent behavioural changes

in different species may however be manifested in a variety of different ways. Classically, rabies has been described as having a prodromal phase followed by either a furious form or a paralytic dumb form. The veterinary professional rarely has the opportunity to observe the animal throughout the clinical course of disease and a clinical diagnosis is often possible after minimal observation, especially in endemic areas where rabies awareness is heightened. A list of clinical signs in rabid animals (in no particular order of frequency) during the various stages of the disease is provided here (Table 2). Some of the signs, such as a change in disposition, may only be noticed after close observation by the owners or persons closely associated with the particular animal.

Table 2. Clinical presentation of rabies in different animals[2].

Domestic dogs	Change in temperament, attacking and biting anything (often injuring mouth and breaking teeth), exaggerated responses to sound and light, restlessness, nervousness, snapping at imaginary flying insects, disorientation, wandering aimlessly, a fixed stare, drooling saliva, hoarse howling, choking sounds, "bone in throat" syndrome, febrile reactions, uncoordinated actions and progressive paralysis, dilated pupils, irritability, photophobia, infliction of self-injury, convulsions, and muscle spasms.
Domestic cats	Generally aggressive, uncoordinated, frothing, muscular tremors, dilated pupils, staring, a threatening posture, abnormal vocalisation, lack of response to owners, unprovoked attacks, biting (sometimes without releasing grip), convulsions, paralysis, coma, hiding away, some cats appear unusually affectionate and purr, or extend and retract their claws.
Cattle	Several animals may have clinical signs at the same time, a typical hoarse bellow, aggressive particularly on provocation, vicious attacks on inanimate objects, biting other cattle, attacking humans, wind-sucking, "bone in throat" syndrome, separate themselves from rest of herd, anorexia, knuckling of fetlocks especially hind limbs, swaying gait, tail and posterior limb paralysis, jaw and tongue paralysis, profuse salivation, dragging hooves, pseudo-oestrous, hypersexual behaviour, decreased milk production, dilated pupils, fixed stare, grinding teeth, pica, tenesmus with diarrhoea, frequent urination, loss of condition, and emphysema.
Sheep/Goats	Symptoms resemble those of cattle but hypersexual behaviour, sexual excitement, incessant bleating, aggression, aimless running, pawing and paddling, and grinding of teeth are prominent.
Horses	Febrile reactions, altered behaviour, biting of wound site, aggression, thrashing, paralysis and inability to swallow.
Pigs	Hiding in corners of the pen, hypersexual behaviour, aggression, biting and may kill offspring.
Wild animals	Often lose fear of humans.
Mongoose	Yellow mongoose generally demonstrate tame behaviour, but some are very aggressive.
Jackal	Jackals are usually aggressive, and lose fear of humans.
Wild cats	Wild cats display similar behaviour to domestic cats. Badgers are usually vicious and fierce.
Antelope	Kudu salivate profusely, may be paralysed, docile, tame, even entering houses. Duiker are sometimes very aggressive.

2.3 Rabies in bats

Rabies disease can be caused by infection with any of the lyssavirus species. The rabies lyssavirus is just one member of the *Lyssavirus* genus, *Rhabdoviridae* family of bullet-shaped viruses with single-stranded RNA genomes. The lyssavirus genus includes a total of 17 rabies-related lyssaviruses at the time of these guidelines. Previously, the Lagos bat lyssavirus (LBV), Mokola lyssavirus (MOKV) and Duvenhage lyssavirus (DUVV) had been reported from SA, with only the latter associated with rare human rabies cases. As recently as December 2020 however, a new lyssavirus species, Matlo bat lyssavirus was also described in bats from Limpopo Province. Human rabies cases remain mostly associated with rabies lyssavirus infection linked to domestic dog exposures.

Rabies virus (this is rabies lyssavirus, previously known as genotype 1 lyssavirus) does not occur in bats outside the Americas, but most other lyssavirus species are present in bats in distinct geographical niches and bat species worldwide. LBV, DUVV, Shimoni and Matlo bat lyssavirus have been detected in certain species of bats in Africa. Human exposure to rabid bats is a rare event and only three bat-related human rabies deaths have been confirmed from Africa. All of these infections were attributed to DUVV. Bats are broadly divided into insectivorous and frugivorous bats with insectivorous bats being generally smaller in size and with ornate facial features. Species diversity is high with more than 200 species present on the African continent; however only eight species have been positively linked to rabies infections to date (Table 3, Figure 2). The vast majority of bat species do not pose a risk of rabies infection and healthy bats do not pose a risk of transmission of the virus. If bats are able to transmit the virus, they behave abnormally, e.g. by flying during the day, being on the ground and showing neurological signs. They will also not survive clinical illness and will eventually die within a few days. Even in the populations of the bat species implicated, a very low percentage of bats pose a risk (estimated to be between 0.1 and 1%). The route of transmission is through contact with infected saliva on broken skin or mucosal membranes with the most common route being a bite. It should be noted that insectivorous bats can weigh as little as 10 g and bite wounds are not always visible. Due to the fatal nature of the infection in the absence of prophylaxis, rabies PEP should be administered even if a clear history of exposure cannot be obtained and direct contact cannot be excluded.

Table 3. Bat species implicated in rabies-related lyssavirus in African countries. Note that biosurveillance in bat species in African countries is limited and this only serves as a guideline and based on the knowledge available to date.

VIRUS	BAT SPECIES IMPLICATED AND TOTAL NUMBER OF INFECTIONS REPORTED	SPILL OVER REPORTED IN THE FOLLOWING SPECIES	COUNTRIES WHERE THE VIRUS HAS BEEN DETECTED
Duvenhage lyssavirus	Associated with insectivorous bat species specifically the Common slit-faced bat (*Nycteris thebaica*) and the Natal long-fingered bat (*Miniopterus natalensis*) have been implicated	Humans	Kenya, South Africa, Zimbabwe
Lagos bat lyssavirus	Mostly associated with frugivorous bats specifically Straw-coloured fruit bat (*Eidelon helvum*), Wahlberg's epauletted fruit bat (*Epomophorus wahlbergi*), Egyptian Rousette bat (*Rousettus aegyptiacus*) and Peter's dwarf epauletted fruit bat (*Micropteropus pusillus*), Only one report from an insectivorous bat Gambian slit-faced bat (*Nycteris gambiensis*)	Cats, dogs and a water mongoose	Central African Republic, Ghana, Kenya, Nigeria, Senegal, South Africa;
Shimoni bat lyssavirus	Associated with only one species of insectivorous bat specifically Striped leaf-nosed bat (*Hipposideros vittatus* now *Macronycteris vittatus*)	None	Kenya
Matlo bat lyssavirus	Associated with only one species of insectivorous bat, specifically the Natal long-fingered bat (*Miniopterus natalensis*)	None	South Africa

a)

b)

c)

d)

Figure 2. Bat species that have been associated with certain lyssavirus species (see Table 3) includes a) the common slit-faced bat; b) the Natal long-fingered bat; c) Eqyptian rousette bat and d) the Wallberg's epauletted fruit bat (Images courtesy of Wanda Markotter, University of Pretoria).

2.4 Diagnosis in animals

Specific laboratory testing is required to confirm a clinical diagnosis of rabies in animals[2]. Laboratory confirmation of the rabies status of an animal that was involved in a possible exposure is helpful in guiding continued post-exposure management decisions, but such decisions should not be delayed while awaiting laboratory findings.

Animals displaying signs of neurological disease, and all stray and wild animals suspected of exposing humans to rabies infection should be euthanised for laboratory investigation. Veterinary Services may choose to hold suspected cats and dogs in quarantine for veterinary observation for a period of at least 10 days. Animals displaying signs of illness during the observation period are then euthanised. A rabies vaccination history may be of some assistance during the assessment but greater reliance should be placed on the clinical picture of the animal. Although the inactivated veterinary vaccines used in SA are known to be extremely effective for periods longer than three years after vaccination, there are numerous compelling reasons for avoiding undue reliance on history of vaccination alone.

For diagnostic purposes, it is essential that a complete history of the animal concerned and the circumstances surrounding the collection of the specimen be supplied to the laboratory[2]. Rabies can be diagnosed from any part of the caudal brain, and in some cases the spinal cord, peripheral nerves and salivary gland. However, it is preferable to submit the entire brain. Samples should be submitted in a leak-proof bottle of 50% glycerol-saline and clearly marked as 'suspected rabies' for the attention of the testing laboratory.

The fluorescent antibody test (FAT) is the standard diagnostic test that is currently used in SA and elsewhere. The presence of rabies virus antigen is demonstrated in brain smears by means of immunofluorescence using anti-rabies fluoresce in labelled conjugates. The FAT is more than 99% reliable when conducted by experienced scientists & technicians.

2.5 Prevention of rabies in animals

2.5.1 Pre-exposure vaccination in animals

There are a number of highly-effective, thermostable, inactivated vaccines commercially available for veterinary use in SA. The duration of immunity conferred varies from one to three years. Specific schedules of vaccination of animals are not presented here.

2.5.2 Post-exposure prophylaxis in animals

PEP of bite contact, unvaccinated carnivores, including domestic dogs and cats is not recommended in SA due limited research and mixed efficacy results in preliminary trials. Therefore, due to the significant public health risk and the invariably fatal consequence of rabies infection in humans, PEP for animals is not recommended.

3. RABIES IN HUMANS

See Annexure 3 for quick guide to human rabies.

3.1 Epidemiology of rabies in humans

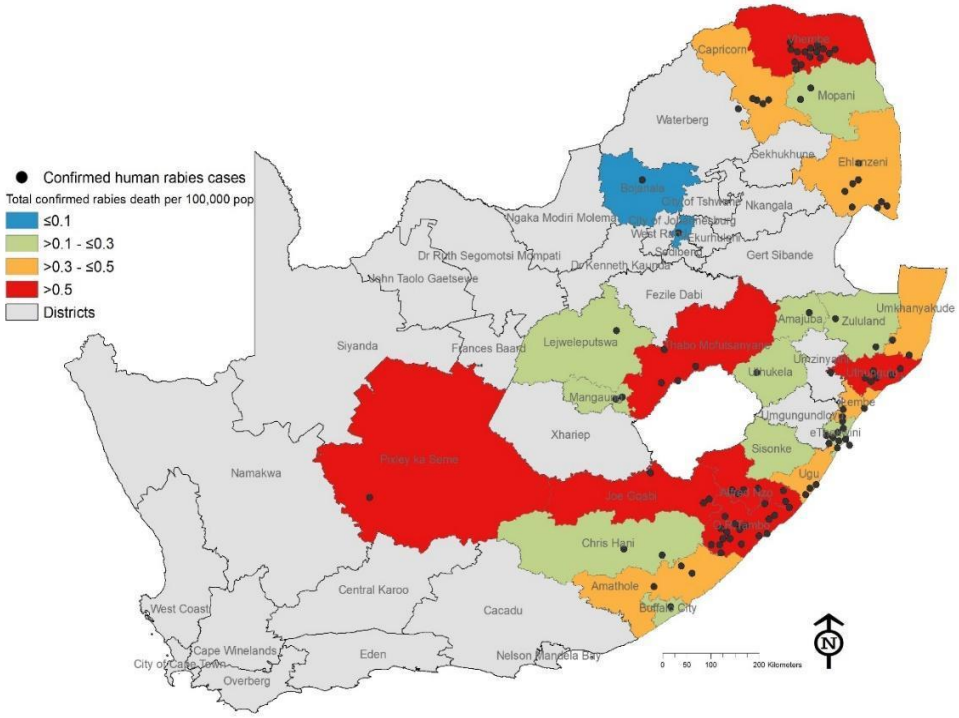


Figure 3. Geographical distribution of laboratory confirmed cases of human rabies in South Africa, 2008-2018 (Map courtesy of NICD).

Human rabies has predominantly been reported from KwaZulu-Natal, Eastern Cape, Mpumalanga, Free State and Limpopo provinces. In the past ten years, an average of 10 human cases (range 1-17) have been reported in SA per year. In 2018, 16 confirmed cases of human rabies were diagnosed from the following provinces: KwaZulu-Natal (n=8); Eastern Cape (n=6), Mpumalanga (n=1) and Free State (n=1). Figure 3 illustrates the distribution of laboratory confirmed human rabies cases in SA from 2008-2018. Note how the distribution of human rabies cases overlaps with the distribution of canine (or domestic dog) cases presented in Figure 1.

3.2 Transmission to humans

The rabies virus is transmitted to humans through virus-laden saliva from a rabid animal. The virus is shed in the saliva of an infected animal, which often hyper-salivates in response to infection, and can be introduced into another body through bites, scratches and any other wounds that transect the skin. Contact of the infected saliva with mucous membranes is also thought to be a possible route of infection, whereas contact of infected saliva with intact skin is not considered an exposure. Human cases are most

often linked to exposures to rabid domestic dogs and few cases involving domestic cats or wildlife species have been reported.

Human-to-human transmission of the virus has been infrequently reported and has been limited to a few cases involving organ and graft transplantation from donors who have died of undiagnosed rabies. Although rabid patients may inflict bites and scratches on healthcare workers, no secondary cases of human rabies have been confirmed or reported following such exposures. The transmission of rabies virus through ingestion has also not yet been reported. This includes the ingestion of meat products or raw milk from confirmed rabid animals. The slaughtering with possible contact of spinal cord, brain and saliva should however be considered for potential risk of exposure to the virus.

3.3 Clinical presentation, diagnosis and treatment in humans

Rabies is fatal upon clinical presentation of the disease, so the focus is on preventing the disease by managing possible exposures to the virus.

The incubation period for the rabies virus (i.e. the period after exposure and before the appearance of signs and symptoms of the disease) varies, but is typically found to be between 20 and 90 days. Rare cases have been associated with shorter or longer incubation periods. During this period, very little (often nothing) may be noted clinically, with few a patients complaining of paraesthesia (tingling or 'pins-and-needles' sensation) and/or pain at the original wound site (or point of entry of the virus in the body). These paraesthesia-like symptoms are more commonly noted when symptoms of clinical rabies commence. In addition to the lack of signs and symptoms of illness during the incubation period, there are no laboratory markers or tests to confirm whether or not an individual has been infected with the rabies virus. The incubation period is followed by the onset of clinical symptoms, which is irreversible. Nearly two thirds of patients develop furious rabies, which may include the following signs: hyperexitability, generalised arousal, hydrophobia, aerophobia, aggression, confusion, etc. The remaining cases present with the paralytic form, which is not unlike Guillain-Barré syndrome. Most patients succumb within a week of the onset of symptoms. Even within an intensive care setting, survival rarely exceeds one month.

Clinical diagnosis is based on the observation of progressive encephalitis in a patient without an alternative confirmed diagnosis. Differential diagnoses for rabies include bacterial/viral meningitis (for example herpes virus infection, arboviral disease), cerebritis or encephalitis (such as cerebral malaria, trypanosomiasis), acute flaccid paralysis (for example poliomyelitis), but also non-infectious causes such as snake bite and psychosis. An epidemiological link involving possible exposure to a rabid animal (for example a dog bite) will strengthen the suspicion of rabies, but such histories are not forthcoming in all cases. There are no informative markers or blood screens that can be investigated to support the diagnosis of rabies. Magnetic resonance imaging may provide some insights, especially for differential diagnoses of other encephalopathies; computed tomography is typically normal and electroencephalography usually shows diffuse slow-wave activity. Specialised laboratory tests for rabies are always required to confirm or exclude the diagnosis. Ante-mortem diagnosis hinges on the detection of viral RNA in saliva, cerebrospinal fluid and/or nuchal biopsies (visit NICD website for more information, www.nicd.ac.za). However, the gold standard for rabies diagnosis remains the detection of rabies virus antigen in post-mortem collected brain

specimens. The direct fluorescent antibody test is widely used for the diagnosis of rabies in animals and in humans, although other tests, such as the direct immunohistochemical test, have also been described for this purpose (visit NICD website for more information).

4. PRE-EXPOSURE PROPHYLAXIS FOR RABIES

Rabies pre-exposure prophylaxis (PrEP) is recommended for individuals at high or continual risk of exposure to the rabies virus as defined by the WHO[1]. Individuals that may be predisposed for exposure to the rabies virus i) due to their occupation (such as veterinarians, other veterinary health professionals, animal welfare workers and laboratory workers), or ii) due to their hobbies such as bat enthusiasts or spelunkers, or iii) due to travel to canine rabies endemic areas where it is expected that rabies PEP may not be accessible if an exposure may occur and/or if particular activities undertaken during the travel will specifically predispose the traveller to possible exposure. The risk for rabies exposure for (ii) and (iii) is assessed on a case-by-case basis.

See Annexure 4 for the 'Prevention of human rabies' poster.

4.1 Regimen for rabies vaccine administration

4.1.1 Intramuscular administration of PrEP

The 2018 WHO position paper on rabies recommends the reduction of PrEP schedule to a two day regimen administered via the intramuscular (IM) route (i.e. days 0 and 7)[1]. See Table 4.

4.1.2 Intradermal administration of PrEP

The WHO recommends intradermal (ID) vaccination as a safe and effective alternative to intramuscular vaccine administration. In order to realise the cost benefit due to dose sparing associated with intradermal vaccination, it is recommended that PrEP be administered where groups of individuals (any group of people of two or more, such a team of veterinarians or a travel group) will receive PrEP at the same time. For example, 1 vial containing 1.0 ml (0.5 ml) dose of vaccine, could ideally be used for up to 10 (5) intradermal doses of vaccine. See Table 4.

4.2 Special considerations

4.2.1 Immunocompromised individuals

Individuals with documented immunodeficiency, such as symptomatic HIV infection, should be evaluated on a case-by-case basis and should receive a complete course of PrEP for immunocompromised individuals: a 3-visit rabies vaccine given either ID (2-sites) or IM (1-site) on days 0, 7 and the third dose given between days 21-28. In the event of possible exposures, full PEP should be provided as described, including the IM schedule of four doses of vaccine and rabies immunoglobulin (RIG) therapy.

4.2.2 Pre-exposure vaccination boosting

It is recommended that individuals at high or continual risk for rabies exposure monitor vaccine-induced rabies immunity by testing rabies antibody titers (see section 4.3). Pre-exposure vaccination boosting is recommended based on the outcome of the serological testing.

4.3 Laboratory testing of antibody titres in vaccinated individuals

Laboratory testing for post-vaccine rabies antibody titres is available in South Africa. Testing of antibody titres is recommended in order to determine if a pre-exposure booster is required to maintain an adequate level of immunological memory to support PEP responses in the event of an exposure. The frequency of testing is based on an assessment considering the risk of exposure to the rabies virus. The WHO recommend testing of antibody levels every two years for individuals such as veterinarians that are at high and continual risk of exposure.[1]

PEP is required in the event of exposure to the rabies virus, regardless of the antibody titre induced by PrEP.

Should a potential rabies exposure occur more than 3 months after a PreP course, rabies vaccine booster doses must be administered.

Table 4. Summary of PrEP regimen for rabies vaccines available in SA.

PRODUCT NAME	DOSAGE	SITE OF ADMINISTRATION	SCHEDULE
i. Verorab™	0.5 ml (per vial) For intramuscular, full vial For intradermal, 0.1 ml per dose	Intramuscular: deltoid muscle in adults **OR** Intradermal*: 1 dose per site, 2 sites per day. Intradermal sites: deltoid muscle, anterolateral thigh or supra scapular region	**Intramuscular:** One dose each on days 0 and 7 **Intradermal:** Two doses each on days 0 and 7
ii. Rabipur™ *Note: This product is currently not available in SA.*	1.0 ml (per vial) For intramuscular, full vial For intradermal, 0.1 ml per dose		

**The intradermal schedule is recommended when PrEP is applied to groups of individuals and a cost benefit would apply (i.e. a single vial represents multiple doses)*

Note: Changes in the route of administration (IM vs. ID) during the same PrEP course are acceptable, if unavoidable, to ensure complete PrEP course.

5. POST-EXPOSURE MANAGEMENT OF POTENTIAL RABIES EXPOSURES

Rabies PEP is the only intervention for human rabies and should be considered an emergency, life- saving medical treatment for potentially exposed individuals.

See Annexure 4 for the 'Prevention of human rabies' poster.

5.1 Wound management

Wounds inflicted by potentially rabid animals are treated as prescribed by the Standard Treatment Guidelines and Essential Medicines List for South Africa.[3] All wounds must be washed and flushed for approximately 5-10 minutes using soap and running water. Apply chlorhexidine (0.05%) or iodine (10%) for disinfection of wounds. Apply additional wound treatment measures (i.e. tetanus booster vaccination, antibiotic treatment, analgesia) as required on a case-by-case basis. Suturing of wounds should be avoided or delayed, unless for urgent haemostasis; and local anaesthetic agents should not be used. This is because suture of wounds and the use of local anaesthetic agents may serve to spread the virus locally.

5.2 Post-exposure prophylaxis

Rabies PEP is considered whenever a patient has been potentially exposed to the rabies virus. A risk assessment should be made on the basis of the health status of the animal and its behaviour in that particular incident, the animal species, the animal vaccination status, the local and provincial rates of rabies, and the bite wound category. See Annexure 1.

5.2.1 Categorisation and management of exposure

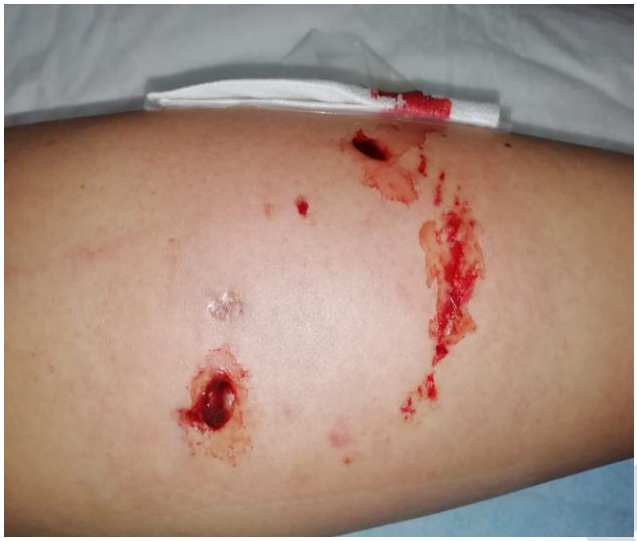
Table 5 provides the algorithm for responding to different types of exposures, and how this relates to PEP management of the patient.

Table 5. Algorithm for rabies PEP for patients with **no history of previous rabies PrEP or PEP.**

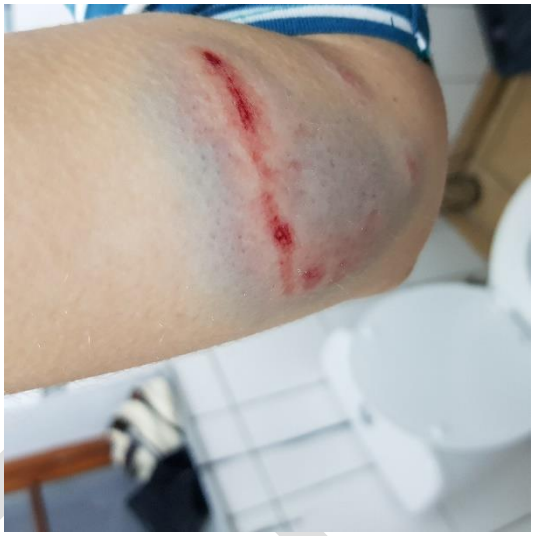
PATIENT WITH ANIMAL EXPOSURE			
Category of the exposure	**Category I** **No direct contact** with animal (for example, being in the presence of a rabid animal or petting an animal)	**Category II** Direct contact with animal but **NO BREACH OF SKIN, NO BLEEDING** (for example bruising or superficial scratch)	**Category III** Direct contact with animal with **BREACH OF SKIN, ANY AMOUNT OF BLEEDING, CONTACT WITH MUCOSAL MEMBRANES** (for example lick on/in eyes or nose)**, CONTACT WITH BROKEN SKIN** (for example licks on existing scratches), **ANY CONTACT WITH A BAT**
Management based on category	WASHING OF EXPOSED SKIN SURFACES	WOUND MANAGEMENT + PROVIDE FULL COURSE OF RABIES VACCINE	WOUND MANAGEMENT + RABIES IMMUNOGLOBULIN + FULL COURSE OF RABIES VACCINE

Examples of category III wounds are shown in Figure 4. Wounds do not have to be large or bleed profusely to be considered as category III. A single drop of blood drawn from the wound indicates a category III exposure. Bat bites, for example, may be very small and not obvious – therefore direct contact with a bat (such as bites or scratches) requires full PEP.

a)



b)



c)

d)

Figure 4. Examples of category III exposure wounds: a) deep puncture wound from a dog bite; b) bruising with bleeding under the skin from a dog bite; c) cat bite and d) scratch marks from a cat, both with no overt bleeding (images courtesy of local veterinarians and animal health technicians).

5.2.2 Regimen for rabies vaccine administration

The recommended regimen for rabies vaccine administration in South Africa is provided in Table 6. The only regimen recommended for post-exposure rabies vaccine administration in South Africa as follows: four doses of vaccine should be administered intramuscularly, one on each day of days 0, 3, 7 and any day between day 14 to 28.

General considerations:

- If there is a known egg allergy, Verorab™ vaccine should be given (rather than Rabipur™ vaccine);
- The dosage for both adults and children is the same (one vial per dose);
- Changes in rabies vaccine product during the same PEP course are acceptable, if unavoidable, to ensure complete PEP treatment;
- Should a vaccine dose be delayed for any reason, the PEP regimen should be resumed (not restarted);
- Rabies vaccines can be co-administered with other inactivated and live vaccines, using separate syringes and different injection sites.

Table 6. Summary of regimen for rabies vaccines available in South Africa

PRODUCT NAME	DOSAGE	SITE OF ADMINISTRATION	SCHEDULE
i. Verorab™	0.5 ml (one vial)	Intramuscular. Deltoid muscle in adults, anterolateral thigh in small children (aged < 2 years)*	One dose each on days **0, 3, 7 and any day between day 14 and 28
ii. Rabipur™ *Note: This product is currently not available in SA.*	1.0 ml (one vial)		

* The dosing for both adults and children is the same.

**Day 0 is the day of presentation to a health facility.

5.2.3 Regimen for rabies immunoglobulin (RIG) administration

Either human-derived rabies immunoglobulin (HRIG) or equine-derived rabies immunoglobulin (ERIG) can be used (see Tables 7 and 8). Due to the potential for anaphylactic reactions with the administration of ERIG, it is recommended that ERIG be used only in facilities where anaphylaxis or adverse reactions can be managed. However, the incidence of anaphylaxis following administration of ERIG is low. Skin testing is not required before the use of ERIG.

The effect of RIG is to immediately neutralise the virus at the wound /exposure site. The immune response to vaccine will only be effective from seven days after the administration of the vaccine. When seven days have lapsed since the initial rabies vaccination, RIG is no longer indicated. This is because the vaccine-induced immune response will be effective after seven days.

The entire calculated dose of RIG should be infiltrated in and around the wound site/s. In the case of smaller wounds/areas where it is not possible to infiltrate the entire calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s without causing compartment syndrome (Tables 7 and 8), (see Annexure 2). According to WHO, evidence has shown that the maximum infiltration of RIG

in and around the wound is effective. It is no longer recommended to inject the remainder of the calculated RIG dose at a site distant to the wound. In case of large and multiple wounds, RIG can be diluted with saline if necessary to ensure infiltration of all wounds.

5.2.4 Management of mucosal exposure

Rinse thoroughly with water for mucosal exposures without wounds. Further rinsing with diluted RIG can be considered on a case-by-case basis. The rabies vaccine course must be completed. If there is a bite site/wound, that area should be infiltrated with RIG.

NB: See Annexure 2 (Example for the dosing of RIG products) to determine the volume (i.e. ml or number of vials) to be administered.

Table 7. Summary of regimen for HRIG products

PRODUCT NAME	MAXIMUM DOSAGE	DESCRIPTION	SITE OF ADMINISTRATION	SCHEDULE
i. Rabigam®	20 IU/kg bodyweight	150 IU/mL Supplied in a 2 mL vial	Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds/areas where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s. See Annexure 2.	On day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated.
ii. KamRAB®	20 IU/kg bodyweight	150 IU/mL Supplied in 2, 5 and 10 mL vials.		

Table 8. Summary of regimen for ERIG

PRODUCT NAME	MAXIMUM DOSAGE	DESCRIPTION	SITE OF ADMINISTRATION	SCHEDULE
i. Equirab®	40 IU/kg bodyweight	200 IU/mL Supplied in a 5 mL vial.	Infiltrate up to the maximum calculated dose in and around the wound site/s. For smaller wounds/areas where it is not possible to infiltrate all of the calculated dose, infiltrate as much as is anatomically feasible in and around the wound site/s. See Annexure 2.	On day 0 (when patient presents for first time)/ as soon as possible after exposure to be effective to neutralise virus. When RIG is not available it should be sourced as a matter of urgency. When 7 days have lapsed since initial rabies vaccination, RIG is no longer indicated.

5.3 Special considerations

5.3.1 Immunocompromised individuals

Individuals with documented immunodeficiency, such as symptomatic HIV infection, cancer patients on chemotherapy/radiotherapy, patients on steroids 20mg/day for ≥2 weeks, should be evaluated on a case-by-case basis and receive a complete course of PEP including RIG (see tables 5-7). In all category II and III exposures, RIG and four doses of rabies vaccine should be administered, one on each day of days 0, 3, 7 and any day between day 14 and 28. **Note:** HIV-infected individuals receiving antiretroviral therapy (ART) who are clinically monitored and well managed are not considered immunocompromised. Such patients have been shown to respond normally to rabies vaccines.

5.3.2 Pregnant and lactating women

Rabies vaccine and RIG are safe and effective in pregnant and lactating women, and should be given if indicated. The dose is the same as for a non-pregnant adult (see tables 6-8).

5.3.3 Patients who have received previous PrEP or PEP

In these individuals, RIG is not indicated. For PEP, only two doses of rabies vaccine should be administered, one on day 0 and one on day 3. Rabies vaccination provides long-lasting immunity. Rabies PEP is not recommended in the event of an exposure within 3 months of completion of PEP. For repeat exposures occurring >3 months after the last PEP, the PEP schedule for previously immunised individuals should be followed; which is two doses of rabies vaccine, one dose administered on day 0 and one on day 3.

5.3.4 Delayed presentation

Rabies PEP should ideally be provided as soon as possible after exposure. When patients present well after the exposure event, consider the first day of presentation as day 0 for vaccine and RIG administration. Where wounds have healed, the RIG can be infiltrated in and around the previous wound site. If RIG has not been given within seven days of the first vaccine dose, it is no longer indicated.

5.3.5 Other exposures

No case of human rabies resulting from the consumption of raw meat from rabid animals has been documented. Infectious rabies virus has never been isolated from milk of rabid cows and no documented case of human rabies has been attributed to consumption of raw milk. In extremely rare cases, rabies has been contracted by inhalation of virus-containing aerosols in laboratories when handling materials that contained highly concentrated live rabies virus, or in caves with a high density of rabies virus infected bats. See Annexure 1.

6. CONTACT DETAILS

Expert advice on prevention of rabies in humans is available from:

- National Institute for Communicable Diseases, a Division of the National Health Laboratory Service:

  For laboratory related queries: 011 386 6339 or 011 386 6376
  For advice on prophylaxis and medical issues, 24-hour clinician hotline: 0800 212 552

- Amayeza, an independent medicine information centre:

  011 475 2994 or 0860 160 160

7. USEFUL LINKS

National Department of Health
www.doh.gov.za

National Institute for Communicable Diseases, a Division of the National Health Laboratory Service:
www.nicd.ac.za

Amayeza Information Services (independent medicine information center):
http://www.amayeza-info.co.za/

Centers for Disease Control and Prevention, United States of America
www.cdc.gov

World Health Organization
www.who.org

Department of Agriculture, Land Reform and Rural development

Information on rabies - https://www.dalrrd.gov.za/Branches/Agricultural-Production-Health-Food-Safety/Animal-Health/information/pamphlets/pamphlet-main

Contact details for provincial state veterinarian services - https://www.dalrrd.gov.za/Branches/Agricultural-Production-Health-Food-Safety/Animal-Health/contacts/provincialveterinary

8. REFERENCES

1. World Health Organization. Rabies vaccines: WHO position paper – April 2018. Available from: http://www.who.int/entity/rabies/resources/who_wer9316/en/index.html (as accessed 15 August 2020).

2. Bishop, G.C., Durrheim, D.N., Kloeck, P.E., Godlonton, J.D., Bingham, J., Speare, R. 2010. *Guide for the medical, veterinary and allied professions*. Second Edition. Pretoria: Department of Agriculture, Forestry and Fisheries. Available from https://www.nicd.ac.za/assets/files/B5_rabies_revised_2010(2)(1).pdf (as accessed 28 August 2020).

3. Standard Treatment Guidelines and Essential Medicines List for South Africa. Primary Healthcare Level, 2020 Edition, National Department of Health, South Africa. Accessed from: https://www.knowledgehub.org.za/elibrary/primary-healthcare-phc-standard-treatment-guidelines-and-essential-medicines-list-south (5 August 2021).

ANNEXURES

ANNEXURE 1: GUIDELINES FOR RISK-ASSESSMENT FOR POSSIBLE RABIES VIRUS EXPOSURE

All animal exposures should be considered for potential rabies risk.

Important factors that assist decision-making on PEP management include details of the nature of the contact and the behaviour of the animal concerned.

Do not delay treatment! It is imperative that prophylaxis be administered as soon as possible after exposure to rabies virus, even before there is laboratory confirmation of rabies in the animal.

Judgement on whether to initiate PEP is assisted by an estimation of risk based on the following criteria, with a high risk of exposure necessitating PEP:

- **Animal involved in the contact**. Domestic dogs and cats are important vectors of rabies virus to humans. All mammalian species may potentially be infected with the virus, however, small rodents e.g. mice and rats commonly found in and around dwellings are not typically associated with rabies. To date, only one transmission of rabies associated with a bite from a baboon has occurred in South Africa. On the other hand, livestock, including cattle, are often reported to be rabid. Snakes and reptiles do not pose a risk for rabies. Bats are an uncommon source of human rabies, and only associated with rabies-related viruses in South Africa. Bat bites may be very small and not obvious – direct contact with a bat (such as bites or scratches) requires full PEP.
- **Animal's behaviour and health**. Healthy animals do not transmit the rabies virus. Animals that may transmit the virus will themselves be affected by the disease. Any abnormal behaviour or signs of ill health in the animal could indicate rabies. Please contact a local veterinarian, state veterinarian or animal health technician to assess the animal.
- **The rabies vaccination status of the animal**. Consider the validity of the vaccination certificate and the timing of vaccination (i.e. if vaccinated in the two weeks preceding the exposure event, may not be immune yet and may have been incubating rabies already at the time of vaccination).
- **The geographical location** of the exposure. Rabies is endemic in South Africa, but the risk of rabies transmission is not the same at all locations.

ANNEXURE 2: EXAMPLE FOR DOSING OF RIG PRODUCTS

Scenario:

It is determined that patient A requires rabies PEP following a category III exposure. The patient weighs 50kg and the product available is HRIG (available in vials containing 150 IU/ml at 2ml per vial). In the scenario, patient A has suffered a) multiple bite wounds; or b) a small transdermal scratch on the ear pinna.

Solution:

Calculate the maximum dose of RIG in IU required for patient A.

We require a maximum dose of 20 IU/kg for HRIG product and the patient weighs 50kg, thus:

20 IU X patient's weight

= 20 IU X 50kg

= 1000 IU required for maximum dose

We know that 1 vial of 2mL contains 300 IU (1 mL = 150 IU), so how many vials do we need to fulfil the maximum dosage?

1 vial of 2mL contains 300 IU
Therefore, Y vials of 2mL contain 1000 IU

Y= 1000/300

= 3.33 vials required for maximum dose

So, a total of 3.33 vials are required to treat patient A with the maximum dosage of RIG. This will equate to a total volume of RIG of 6.66 ml (i.e. 3.33 X 2 ml/vial).

For scenario a (i.e. multiple bite wounds), infiltrate the product in ALL wounds (the product may be further diluted with normal saline to ensure that ALL wounds are reached).

For scenario b (i.e. a small transdermal scratch on ear pinna), it may not be possible to infiltrate the maximum volume of RIG calculated due to the size and location of the wound without risk for compartment syndrome. **It is important to infiltrate as much RIG, up to the maximum dose, even in small wounds.**

For small wounds, it is suggested that one vial be opened and used at a time to avoid wastage (up to the maximum number of vials calculated) and wound infiltrated as much as possible without compromising blood supply. This is important to avoid compartment syndrome. As much of the calculated dose of RIG as possible, should be infiltrated into and around the wound/s.

ANNEXURE 3: RABIES QUICK REFERENCE GUIDE

RABIES

Quick Reference Guide

03 February 2021

Rabies is 100% fatal but 100% preventable in humans with prompt and complete post-exposure prophylaxis (PEP). All animal exposures must be assessed for potential rabies virus exposure and whether rabies PEP is required. Rabies PEP consists of a course of rabies vaccine and rabies immunoglobulin (RIG), if indicated. All wounds have to be immediately washed and flushed for approximately 15 minutes using water, or preferably soap and water.

Delayed presentation

Rabies PEP should ideally be provided as soon as possible after exposure. If the patient presents well after the exposure event, consider the first day of presentation as day 0 for the administration of RIG and vaccine. If the wounds have healed, RIG can be infiltrated into and around previous wound sites.

Wounds on high risk sensitive areas

Wounds on the face, eyelid, scalp, ear and similar sensitive areas pose a challenge for local administration, especially in children. All wounds on the face are high- risk and rabies disease may develop after a short incubation period. It is **CRITICAL** in these cases that RIG is infiltrated **INTO THE WOUNDS.**

If RIG is not available at the time of presentation

If RIG is not available at first visit, it should be sourced as a matter of urgency; however, its use can be beneficial up to seven days from the date of the first vaccine dose. The vaccine-induced immune response will be effective after seven days.

Where to give RIG for mucosal splashes

In case of mucosal exposures without a wound, rinse the area thoroughly with water, active immunisation with a vaccine course is recommended. Lavage of the area with RIG has been used but this is not an evidence- based recommendation.

Multiple wounds

RIG must be infiltrated into every wound. If needed, dilute the RIG with normal saline to ensure sufficient volume to infiltrate all the wound areas.

Pregnant and lactating women

Rabies vaccine and RIG are safe and effective in pregnant and lactating women, and should be given if indicated. The dose is the same as for a non-pregnant adult.

Missed doses

Should a vaccine dose be missed for any reason, the PEP regimen should be resumed (not restarted), adhering to the minimum intervals between doses.

Consumption of raw meat and milk from a rabid animal

No case of human rabies resulting from the consumption of raw meat from rabid animals has been documented. The rabies virus has never been isolated from milk of rabid cows and no documented human rabies case has been attributed to consumption of raw milk.

Immuno-compromised individuals

Individuals with documented immunodeficiency, such as symptomatic HIV infection, should be evaluated on a case-by-case basis and receive a complete course of PEP including RIG. Irrespective of category of exposure or previous vaccination history, RIG and four doses of rabies vaccine should be administered, one on each day of days 0, 3, 7 and any day between day 14 and 28.

SA rabies guidelines are available at

www.nicd.ac.za under the 'Diseases A-Z' tab

ALTERNATIVELY: CALL NICD HOTLINE 0800 212 552

ANNEXURE 4:

Printable copy available from NICD website, www.nicd.ac.za/rabies

PREVENTION OF RABIES IN HUMANS

RABIES IS 100% FATAL BUT 100% PREVENTABLE IN HUMANS
WITH PROMPT AND COMPLETE POST-EXPOSURE PROPHYLAXIS (PEP)

RABIES EXPOSURE RISK ASSESSMENT

- All animal exposures must be assessed for potential rabies virus exposure and whether rabies PEP is required.
- Risk assessment is based on behaviour and health status of the animal, animal species, and geographical area where the exposure took place. Vaccination history of the animal may be unreliable, if in doubt, provide PEP.
- High risk rabies incidents may include: unprovoked animal attack; animal with unusual behaviour e.g. domestic animals becoming aggressive and wild animals appearing 'tame'; sick animal e.g. drooling, wobbling/unsteady gait, snapping at imaginary objects, and/or animal having died within 2 weeks after the human attack.
- Rabies is not transmitted by birds or reptiles. Low risk species in South Africa (RSA) include mice, rats, squirrels, monkeys and baboons.
- Do not delay PEP pending laboratory confirmation of rabies in an animal – PEP may be discontinued if results are negative for the animal involved.

MANAGEMENT OF PATIENT

General wound management is critical in all patients:

- Flush well with soap and water for at least 5 - 10 minutes, then clean with chlorhexidine solution (0.05%). Disinfect with iodine solution/ointment.
- Avoid or delay suturing (where possible) and use of local anesthetic agents (may potentially spread the virus locally).
- Provide antibiotics (e.g. amoxicillin clavulanate) and/or tetanus vaccination as required.

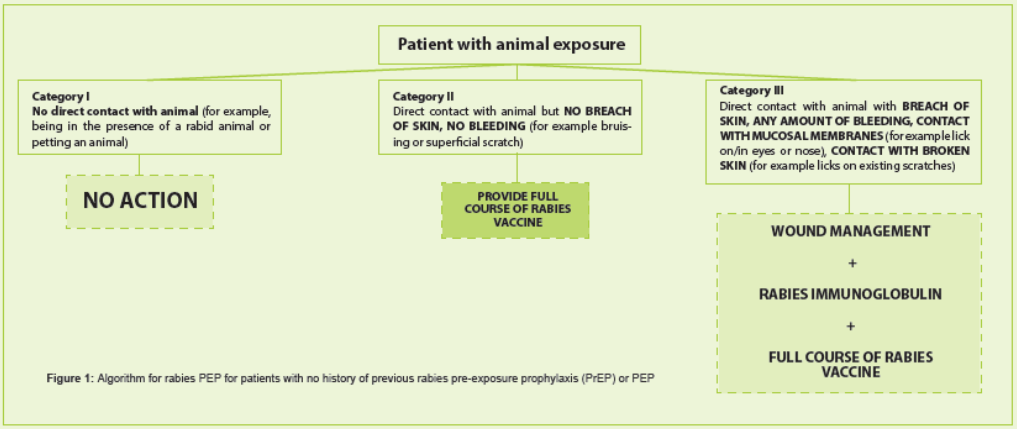


Figure 1: Algorithm for rabies PEP for patients with no history of previous rabies pre-exposure prophylaxis (PrEP) or PEP

RABIES VACCINE

- Vaccination schedule requires FOUR doses.
- Course: days 0, 3, 7 and any day between day 14 and 28 (Day 0 = day of first vaccination).
- Intramuscular injection in deltoid muscle in adults, anterolateral thigh in small children (< 2 years of age). INEFFECTIVE IF GIVEN IN GLUTEUS MAXIMUS (buttocks).
- Vaccine dose: 1 vial equals one dose (regardless of vial size) for adults/children.

RABIES IMMUNOGLOBULIN (RIG)

- Dose of RIG: 20 IU (human derived RIG products) or 40 IU (equine derived RIG products) per kilogram of body weight (i.e. calculate for each case). Infiltrate RIG in and around wounds, giving as much as anatomically possible without compromising blood supply (especially for extremities).
- Evidence has shown that maximum infiltration of RIG in and around the wound is effective and that there are no benefits from additional intramuscular administration of any remaining RIG at a site distant to the wound.
- If multiple wounds, dilute RIG in equal volumes of saline and infiltrate all wounds.
- Different strengths/preparations for the RIG products are available. Check the package insert of all RIG products to ensure that the right dosage and volume is administered.
- RIG provides immediate immunity and is administrated as soon as possible but not beyond 7 days after administration of first dose of vaccine (for example, if not available at clinic, needs to be urgently sourced).

SPECIAL CONSIDERATIONS

- **Immunocompromised:** Symptomatic HIV infection or other documented immunodeficiency, in category II and III exposures, provide full course of vaccine and RIG, regardless of previous rabies vaccination history.
- **Pregnant women & children:** No contraindication to vaccine or RIG.
- **Individuals who have been vaccinated for rabies before:** No RIG required. For PEP, give booster vaccination (Course: days 0 and 3) (irrespective of pre-exposure vaccination antibody titer).
- **Individuals at high or continual risk for rabies exposure (such as veterinarians):** Provide pre-exposure vaccination comprising 2 doses of vaccine (Course: Day 0 and 7). Monitor antibody over time through serological testing.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

MORE INFORMATION:
NICD website: www.nicd.ac.za
NICD Hotline for Clinical Advice: 0800 212 552
Updated: SEPTEMBER 2021

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Adapted from: Rabies vaccines; World Health Organization Position Paper - April 2018. Available from http://apps.who.int/iris/bitstream/handle/10665/272371/WER9316.pdf?ua=1