

SECOND EDITION 2010

RABIES

GUIDE FOR THE MEDICAL, VETERINARY AND ALLIED PROFESSIONS

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D.N. Durrheim
P.E. Kloeck
J.D. Godlonton
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R. Speare
Rabies Advisory
Group 2000



agriculture,
forestry & fisheries

Department:
Agriculture, Forestry and Fisheries
REPUBLIC OF SOUTH AFRICA

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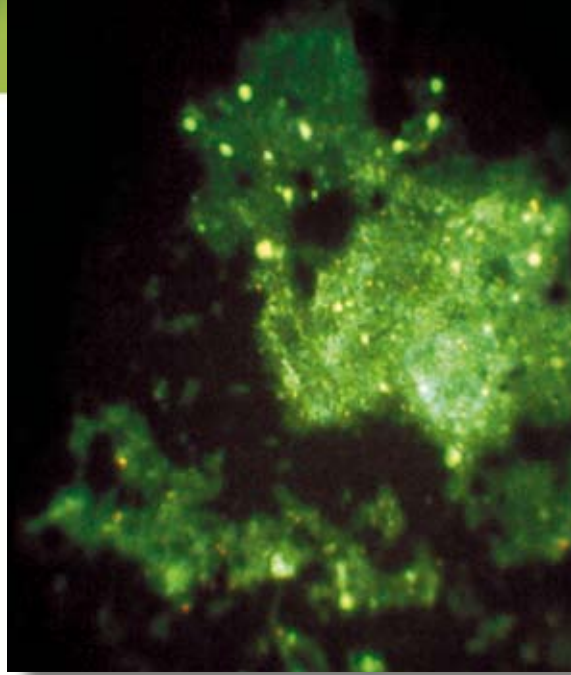
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Cover photo: Brain material, stained with anti-rabies fluorescein conjugate, containing large numbers of oval-shaped, apple-green Negri bodies

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Guide for the Medical, Veterinary and allied Professions

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TRIBUTE TO GEORGE BISHOP



This publication is dedicated to the memory of our gifted and unique fellow-author, colleague and friend.

He passed away tragically and unexpectedly on 25 August 2001. These guidelines are dedicated to George's selfless contribution to rabies control and his burning passion to prevent human suffering in marginalised communities that bear the brunt of this terrible disease.

This was a poignant exercise. Careful review of structure, sentences and even individual words provided vivid recollections of George's expansive sense of humour, attention to detail and tenacious pursuit of accuracy. Although this endeavour was shrouded by the painful realisation that despite our most valiant efforts, we could never hope to emulate George's writing and editing skills, we were, however, encouraged in this venture by an acute knowledge that he would have wished it completed even if only a single rabies death could thereby be averted.

The veterinary and public health fraternities have lost a highly respected and a beloved friend. He was the unlauded hero of rabies control in Africa and certainly did not receive the due credit during his lifetime.

All who knew George are profoundly grateful for having had this privilege. His family's deep sense of loss is shared by all his colleagues and friends, in particular the Rabies Advisory Group.



FOREWORD

Rabies is a disease of animals but too often the outcome is gauged in terms of human suffering and death. Despite this, in areas of the world where rabies is endemic there is often a lack of communication between veterinary and medical professionals, to the extent that the disease continues to thrive and potential victims are not treated. The problem is partly exacerbated by a lack of awareness and experience of the disease and of what to do when confronted by suspect cases. In these technologically advanced days, although it is possible to learn “all there is to know” about almost any subject, it is sometimes difficult to distil the essence.

In most parts of the world, rabies is endemic in either dogs (canine rabies) or in wildlife species (sylvatic rabies). South Africa is one of only a few countries where both forms of the disease occur. Indeed, not only does South Africa have to contend with canine and therefore human rabies, but the sylvatic form of the disease is present in canids, such as jackals and bat-eared foxes, and in viverrids, such as mongooses and in bats.

For many years the South African Rabies Advisory Group (RAG) has worked assiduously to raise awareness of rabies to government agencies, local medical and veterinary professionals as well as to the public. Much has been published, videos have been prepared, surveillance and diagnostic systems have been put in place, treatment centres established and vaccine made available.

This publication on rabies has been prepared for distribution to the medical, veterinary and allied professions. It is written, not only from the vast volume of rabies literature available, but drawn from the experience of those who have been involved in the fight against rabies in South Africa over many years. The scientific information has been thoroughly researched and critical points are emphasised on each page.

In the chapter ‘Rabies in animals’, attention is drawn to the importance of accurate identification of suspect

species, because the species involved in a rabies incident may have a bearing on decisions concerning the treatment of potential victims and/or control policies. The publication contains clear pictures of the terrestrial mammal species which have been found rabies positive in South Africa. Also in this part are sections on diagnosis, prevention and the procedures to be followed when rabies is suspected.

Human rabies is dealt with in depth. Again, prevention and procedures to be followed are highlighted and there is an especially relevant section on management of humans exposed to rabies, a terrain that is not always covered in textbooks on rabies. Of special relevance to South Africa are the sections on rabies legislation and control strategies.

Above all else, this is an instructive manual, with a welcome absence of any attempt to ‘blind with science’. No one should be put off by the word ‘Professions’ in the title, it is eminently readable by the interested layman. It is relevant to and deserves a wider audience than South Africa alone, because the information is applicable to many southern and eastern African countries. It successfully bridges the gap between the mysticism and ignorance that surrounds rabies and the hard fact that it is one of the most deadly diseases known to man.

Written by the late Arthur King – Former Rabies Research Leader, Weybridge, United Kingdom.

This publication is dedicated to his memory with profound gratitude for his contribution in the field of rabies.

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Acknowledgement is especially due to the parents who granted permission for publication of the photographs of their children appearing in this publication. Their contribution towards the fight against rabies is sincerely appreciated.

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Any omission in acknowledgement is regretted. This manual is made available for the express purpose of medical, veterinary and nursing training and education.

INTRODUCTION

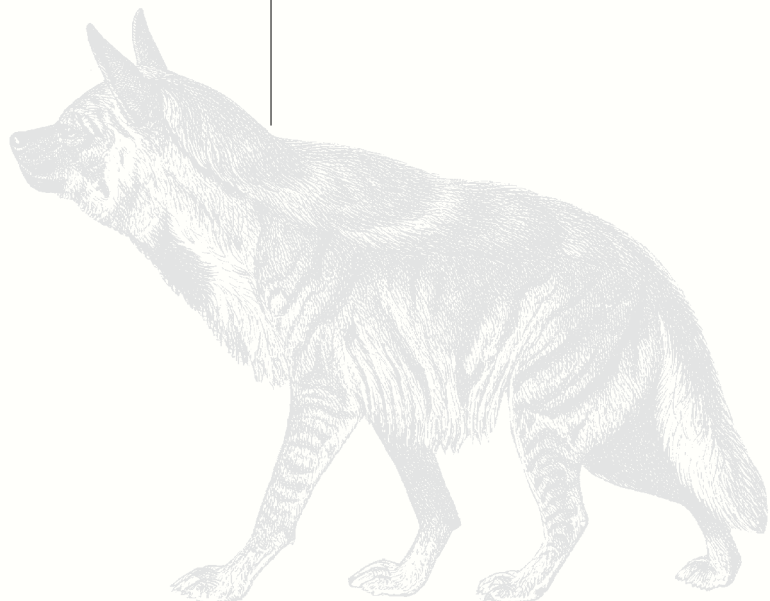
Rabies, a fatal disease of humans and all other mammals, is caused by a virus which has been associated with animal bites for more than 3 000 years and it is the oldest infectious disease known to medical science.¹ Dogs have long been recognised as the main transmitters of the disease to people.^{2,3} When compared with other formidable human diseases such as bubonic plague and smallpox, and animal diseases such as rinderpest and anthrax, rabies has probably never caused comparably high numbers of deaths in humans and animals. However, the horrendous manner in which rabies manifests itself in its victims continues to attract the attention of scientists, health and veterinary workers. The true scale of rabies in South Africa remains clouded by the many thousands of people protected by post-exposure treatment each year after rabies exposure and the undiagnosed human and animal rabies cases not reflected in official statistics.

Animal rabies is endemic throughout South Africa and the disease is currently responsible for the laboratory confirmed deaths of between 10 and 30 people each year. Tragically, with very few exceptions, those who succumbed to the disease over the past decade did not

receive the correct post-exposure prophylaxis and died following bites by rabid dogs.

There have been several new and exciting developments in our knowledge of the disease and in measures used to control rabies in South African animals. The use of monoclonal antibody typing, together with gene sequencing technology, have revealed several different strains of the rabies virus, some of which appear to show clear host preferences. The entire country was declared rabies-endemic during 1999 and it is now compulsory for all dogs and cats to be vaccinated at least once every three years.

Since 1994, the national Rabies Advisory Group (RAG) has reviewed advances in rabies management and control, and made recommendations on control policy. The RAG's suggestions were ratified by the Interprovincial Veterinary Working Group (national and provincial veterinary directors) and the Department of Health. This publication represents the RAG's effort to enhance awareness of rabies, improve pre- and post-exposure measures for humans and the control of rabies in animal populations of the country.



RABIES IN SOUTH AFRICA

Historical aspects

Rabies may have existed as a disease entity in South Africa for more than a century. There is anecdotal evidence of human disease, as a result of wild animal exposure, in the mid-19th and early 20th centuries.⁴ The disease was first confirmed in dogs, by rabbit inoculation, in 1893 but this relatively small outbreak was thought to have followed the importation of an infected owned dog from England during the previous year. The outbreak was rapidly controlled by muzzling dogs, introducing movement control and destroying strays. The disease apparently did not spill over to wild animals. Endemic rabies was first confirmed in 1928 following the deaths of two children who had been bitten by a yellow mongoose in the Wolmaranstad district of the North West Province.⁵ The existence of four genotypes of lyssavirus in Africa is considered by some to be strong circumstantial evidence that the continent was the cradle of lyssavirus evolution.^{6,7,173}

The occurrence of endemic “herpestid” (previously referred to as “viverrid”) mongoose rabies is closely associated with the distribution of the yellow mongoose. This species occurs widely on the central plateau of the country. Attempts at depopulation of yellow mongooses proved prohibitively expensive and largely ineffectual, and were halted by the end of the 1970s. This small mongoose often lives in close proximity to ground squirrels and suricates (Plate 1). The number of ground squirrels and suricates found to be rabid is probably lower than might be expected, but in the field there is often confusion with species identification. Erroneous nomenclature has often arisen from language translations and colloquial misnomers.

There is no firm evidence that canid (canine) rabies was important in South Africa prior to the late 1940s.¹⁸ The occasional rabid dog is thought to have been infected through contact with the endemic mongoose form of the disease. Veterinary authorities were, however, aware of a more invasive form of rabies that existed in Namibia and Botswana prior to 1950. Dog rabies was confirmed in 1950 in the



Plate 1: Suricates (above) often live in close proximity to yellow mongoose colonies and are frequently diagnosed rabid

Limpopo Province and reached Zimbabwe later that year. Establishment of infection in the black-backed jackal population has resulted in the disease remaining endemic in the northern parts of South Africa ever since (Plate 2). Records indicate that the prevalence of bovine and jackal rabies is closely associated in these areas. After spreading through Mozambique from 1952, the first cases of dog rabies in KwaZulu-Natal, which had previously been free of the disease, were diagnosed in 1961. Vigorous control measures, including vaccination and destruction of stray dogs, were enforced by the local veterinary authorities who successfully eliminated the disease by the end of 1968. The reappearance of rabies in KwaZulu-Natal in 1976 and its subsequent endemicity was associated with the migration of refugees from Mozambique. Subsequently rabies incidence has been exacerbated during periods of sociopolitical instability and drought. The situation deteriorated with the division of veterinary authority, inability to control dog movement and often inadequate vaccine coverage in the more densely populated areas. Factors such as the prevalence of AIDS especially in rural communities may affect



Plate 2: Black-backed jackal are common in the northern regions of South Africa where they are important rabies vectors

the habitation of domestic dogs, with ownerless dogs forming feral packs that hunt for food and reportedly even attacks human victims. There is evidence for the movement of rabies northwards from KwaZulu-Natal into south-eastern Mpumalanga and southwards into areas of the Eastern Cape Province, likely following the large-scale migration of families and their pets.¹⁵⁷

The bat-eared fox appears to be the dominant maintenance host in the western areas of South Africa.¹⁷⁴ Rabies is also diagnosed frequently in black-backed jackal in the northern parts of the country. An outbreak of rabies in kudu antelope in Namibia (1975-1985) led to the loss of an estimated 30 000 to 50 000 animals. Another outbreak followed in 2002 and an excess of 2 000 animals were lost. Although the virus associated with these outbreaks are closely related to the canid virus associated with black-backed jackals, it is speculated that an unique large scale interherbivorial spread may occur among the kudu.¹⁵⁸

Rabies and rabies-related viruses

The causative agent of rabies is a member of the Lyssavirus genus of the Rhabdoviridae family of bullet-shaped viruses, which has a single-stranded RNA genome. The genus includes the classical rabies virus (genotype 1) and presently six so-called rabies-related viruses, Lagos bat virus (genotype 2), Mokola

Three of six rabies-related viruses, namely Mokola, Lagos bat and Duvenhage viruses have been isolated in South Africa to date

virus (genotype 3), Duvenhage virus (genotype 4), European bat lyssaviruses 1 and 2 (genotypes 5 and 6), and Australian bat lyssavirus (genotype 7).^{3,8,159} Several novel lyssaviruses from Eurasia have been described recently and await taxonomic classification.¹⁵⁹

Three of the rabies-related viruses, namely Mokola, Lagos bat and Duvenhage viruses have been isolated in South Africa to date (Table 1). Mokola was also isolated in neighbouring Zimbabwe from six cats and a dog, and Lagos bat virus was found in a cat in the same country. Lagos bat virus has not been associated with human disease whereas Mokola was isolated from the brain of a girl who died from paralytic disease in Ibadan, Nigeria during 1971 but the source of infection was not established.^{3,9,10} The two cats from which isolations of Lagos bat virus were made in South Africa and Zimbabwe, had both been vaccinated against rabies. The Zimbabwean cat manifested lethargy and paresis without any aggression. In contrast, all five cats (four of which had been vaccinated against rabies) from which Mokola virus has been isolated since 1996 in South Africa, displayed aggression when handled. Recently the first isolation of Lagos bat virus from terrestrial wildlife, namely a water mongoose was confirmed.¹⁷⁵ Mokola virus has yet to be isolated from a bat and there is still no evidence that rabies-related viruses have adapted to spread in carnivores. To date, infection of bats with classical rabies virus (Lyssavirus 1) has only been confirmed to occur in the Americas.¹¹

Table 1: Cases of rabies-related viruses in South Africa

Location	Year	Host	Virus
Pinetown and Durban, KZN ¹²	1980	Fruit bats (<i>Epomophorus wahlbergi</i>)#	Lagos bat
Stanger, KZN ¹³	1982	Cat	Lagos bat
Durban, KZN ¹⁴	1990	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Durban, KZN ¹⁸²	2003	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Richards Bay, KZN ¹⁸⁵	2003	Canine	Lagos bat
Durban, KZN ¹⁸²	2004	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Durban, KZN ¹⁷⁵	2004	Water mongoose	Lagos bat
Durban, KZN ¹⁸²	2005	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Durban, KZN ¹⁸²	2006	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Durban, KZN**	2008	Fruit bat (<i>E. wahlbergi</i>)	Lagos bat
Bela-Bela, Limpopo ¹⁵	1970	Human	Duvenhage
Louis Trichardt, Limpopo ¹²	1981	Insectivorous bat	Duvenhage
Near Rustenburg, North West ¹⁶⁰	2006	Human	Duvenhage
Umhlanga Rocks, KZN ¹²	1970	Cat	Mokola
Mdantsane, Eastern Cape ¹⁷	1995	Cat	Mokola
East London, Eastern Cape ¹⁶	1996	Cat	Mokola
Yellow Sands, Eastern Cape ¹⁷	1996	Cat	Mokola
Pinetown, KZN ¹⁷	1997	Cat	Mokola
Pinetown, KZN ¹⁷	1997	Cat	Mokola
Pietermaritzburg, KZN ¹⁷	1998	Cat	Mokola
Nkomazi, Mpumalanga ¹⁷¹	2005	Dog	Mokola
East London, Eastern Cape ¹⁷¹	2006	Cat	Mokola
Stonehills, Eastern Cape***	2008	Cat	Mokola

* KZN = KwaZulu-Natal

** Personal communication: Dr W Markotter, University of Pretoria

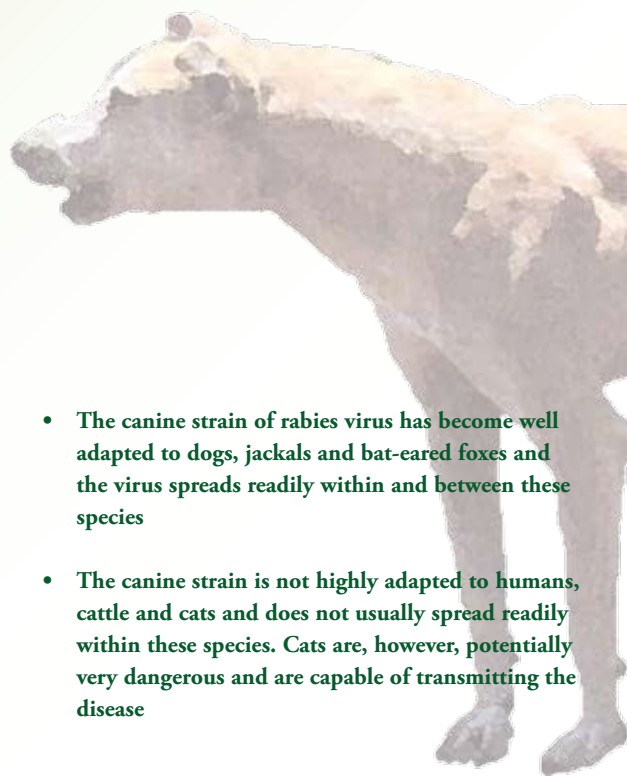
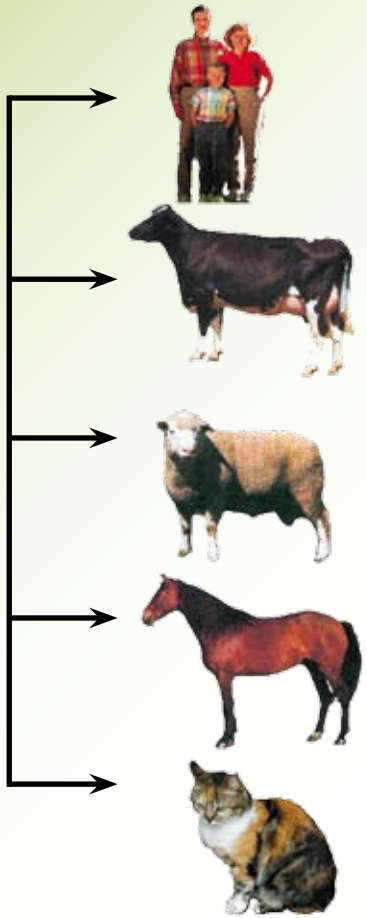
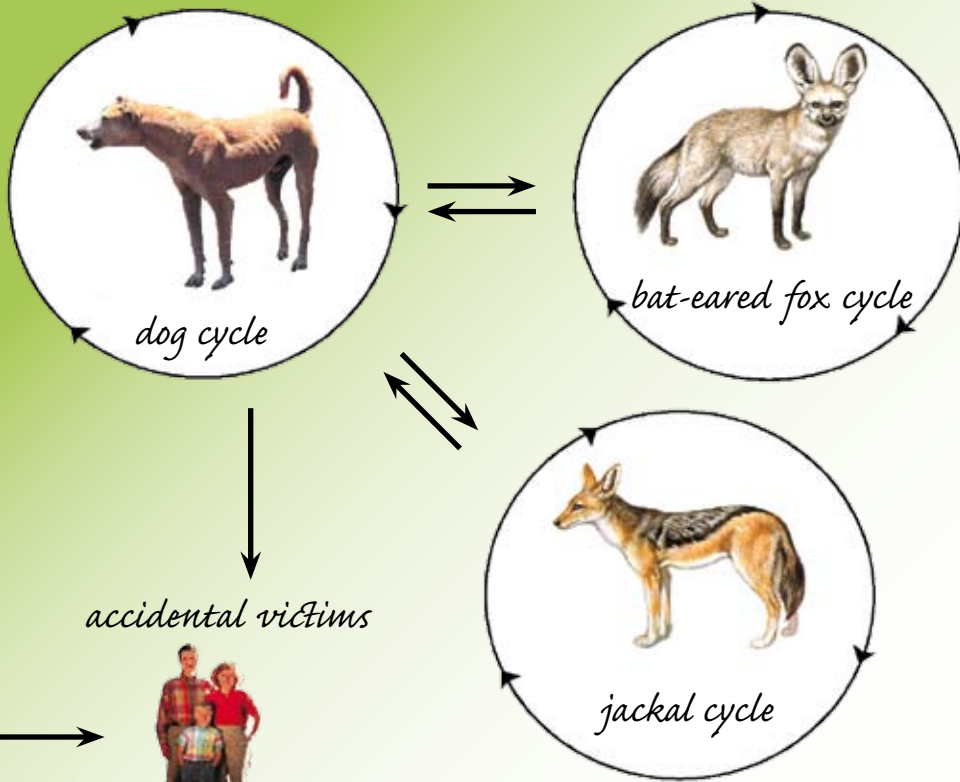
*** Personal communication: Dr C Sabetta, Agriculture Research Council, Onderstepoort Veterinary Institute

Thirteen fruit bats tested positive with the fluorescent antibody test but only three virus isolates were obtained

In February 1970, an adult male patient from Bela-Bela (formerly Warmbaths), approximately 100 km north of Pretoria, died after a five day illness, which was diagnosed clinically as rabies. Infection was thought to have taken place following a bite on the lip from a bat, thought to be an insectivorous species.¹⁵ This index virus was subsequently typed as Duvenhage virus and a further isolation has subsequently been made from a bat in South Africa during 1981.¹² In 2006 a patient died of rabies after an encounter with a bat in the North West province in South Africa. The etiological agent was confirmed to be Duvenhage virus. The exposure occurred about 80 km from where the first exposure occurred 36 years earlier.¹⁶⁰ The first reported case of Duvenhage virus infection outside of Southern Africa was confirmed in 2007. A Dutch tourist was scratched by what was thought to be an insectivorous bat at a camping site in Kenya. She developed signs of rabies about 3 weeks after the exposure and died in a hospital in Amsterdam 23 days later.¹⁷⁶

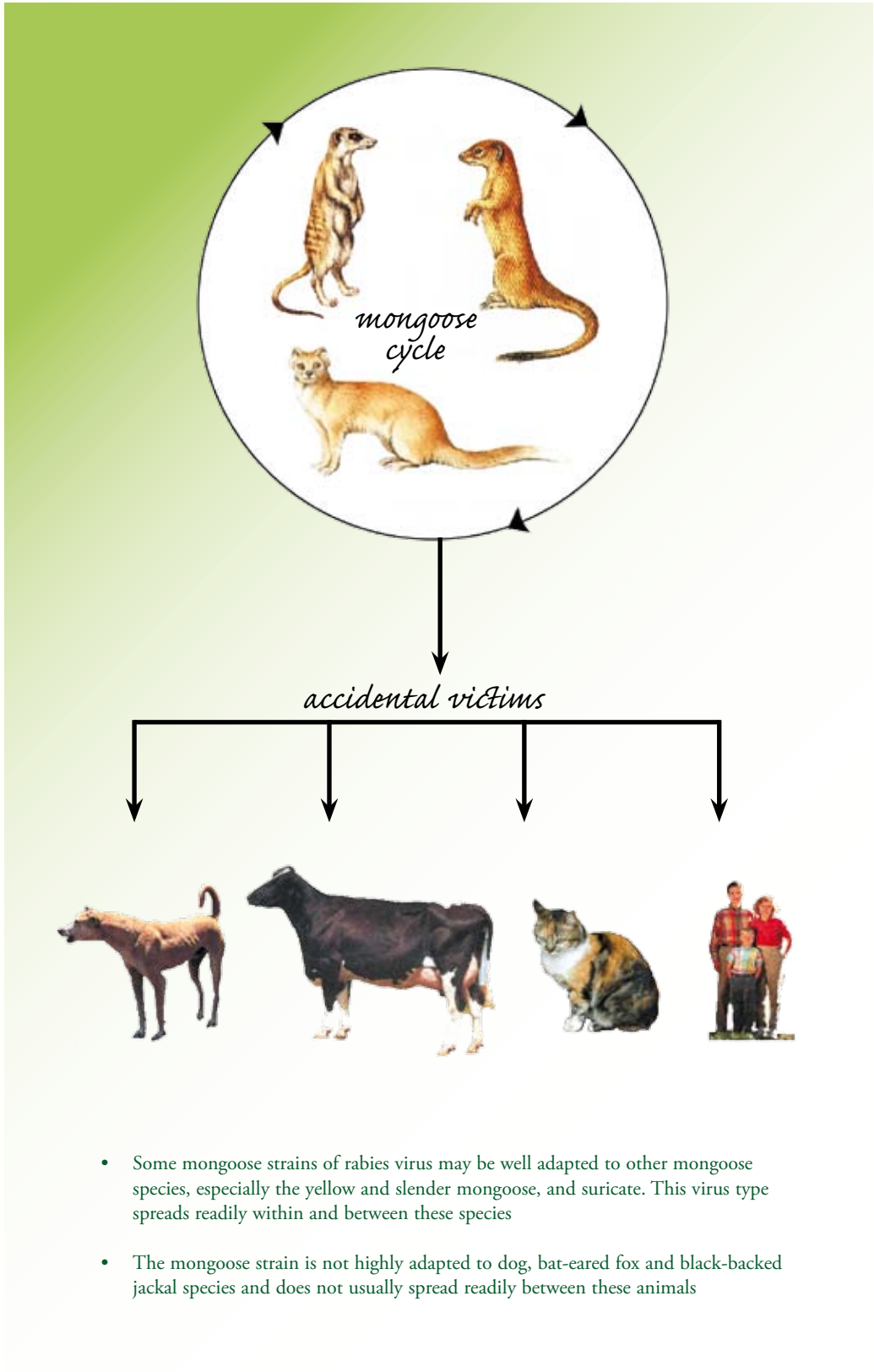
Rabies virus is antigenically most closely related to the Australian bat Lyssavirus and most distant from Lagos bat virus, Mokola virus and West Caucasian bat virus (a newly described lyssavirus), in this order.^{8,18,177-179} An illustration of the distant relationship between rabies virus and these viruses is the fact that standard rabies vaccination as well as post-exposure prophylaxis gives little to no protection against these viruses.¹⁸⁰⁻¹⁸¹ In the absence of specific vaccines and immunoglobulins it is reasonable that standard rabies vaccine and immunoglobulin be used in all instances of potential exposure to rabies-related viruses.

Over the past 20 years an important development has been the recognition, through monoclonal antibody and gene sequencing studies, that genotype 1 viruses which cycle in particular host species and often within distinct geographic regions, tend to undergo genetic adaptation resulting in the development of biotypes.^{14,19,20} These biotypes, which have subtle



- The canine strain of rabies virus has become well adapted to dogs, jackals and bat-eared foxes and the virus spreads readily within and between these species
- The canine strain is not highly adapted to humans, cattle and cats and does not usually spread readily within these species. Cats are, however, potentially very dangerous and are capable of transmitting the disease

Fig.1: An illustration of canid rabies virus strain cycles in various species



- Some mongoose strains of rabies virus may be well adapted to other mongoose species, especially the yellow and slender mongoose, and suricate. This virus type spreads readily within and between these species
- The mongoose strain is not highly adapted to dog, bat-eared fox and black-backed jackal species and does not usually spread readily between these animals

Fig. 2: An illustration of possible mongoose rabies virus strain cycles in various species

unique differences in antigenicity and pathogenicity, may become adapted to a particular host species. This species may then become the maintenance host, permitting the spread of infection to other species. A diagrammatic representation of this cycle in dogs is provided in Fig. 1. A hypothetical diagram of mongoose cycles is depicted in Fig. 2. The major host species recognised in South Africa are the dog, yellow mongoose, black-backed jackal and bat-eared fox (Fig. 3). Two biotypes of rabies virus are described in Southern Africa.^{14,161} The canine strain is less variable than the mongoose strains and has been most frequently isolated from dogs, bat-eared foxes and black-backed jackal.^{21,162,163} There are several mongoose virus strains and they are associated with the yellow mongoose, slender mongoose, suricate and ground squirrel. Mongoose virus does not have the same propensity for epidemic spread in dogs as the canid biotype.^{18,163}

Pathogenesis and immunity in humans and animals

Pathogenesis

Rabies virus gains entry into a new host by introduction of virus-containing saliva into a bite wound. Entry may also be gained by saliva contamination of the mucous membranes of the mouth, eyes and nasal passages. The virus does not penetrate intact skin.²² At the site of entry, there may be local viral proliferation in non-neural tissue followed by viral attachment to nerve cell receptors and entry into peripheral nerve endings.²³ The virus is transported along afferent axons, eventually reaching the central nervous system where proliferation is followed by widespread distribution of the virus throughout the brain and spinal cord. Following centrifugal transport along efferent cranial nerves, the salivary glands become infected and virus particles are shed in the saliva. Infection of the brain commonly leads to behavioural changes that induce the host to bite other animals, thereby transmitting the virus. The clinical picture can be highly variable between different species, individuals of the same species, and even within the course of the disease in a particular individual. The widespread central nervous system infection almost inevitably leads to death, usually through



Plate 3: Severe facial lacerations in a child caused by dog bites. Children are frequently victims of dog bites. Facial bites usually result in much shorter rabies incubation periods

respiratory paralysis, but also through secondary circulatory, metabolic or infectious processes.

However, the virus may be shed before the appearance of clinical signs. During most of this incubation period, the virus is in transport along axons.²⁴ However, in exceptionally long incubation periods, lasting more than four months, it is thought that the virus may remain latent, probably at the site of introduction before entry into the peripheral nervous system.²⁵

Shedding of virus in saliva usually occurs simultaneously with, or soon after, the appearance of clinical signs

The length of the incubation period is affected by several factors. Bite sites in close proximity to the brain, such as those on the head, tend to have shorter incubation periods. Likewise, deep or very severe bites, where a higher dose of virus is introduced, have a greater probability of disease development and shorter incubation periods.²² Once the virus is affecting the central nervous system and its function, the clinical course is acute

Shedding of virus in saliva usually occurs simultaneously with, or soon after, the appearance of clinical signs and progressive with death usually within 10 days in animals and five days or less of the onset of rabies symptoms in humans (J.D. Godlonton, personal communication).

Following central nervous system infection, the virus is transported centrifugally along cranial nerves and along motor and sensory pathways as well as the spinal cord. This results in the presence of viral particles in peripheral nerve tracts in many tissues, particularly those of the head. Therefore, a diagnosis of rabies may sometimes be possible by examination of skin sections, where antigen can be detected within nerve tracts, or corneal smears.^{26,27}

Rabies virus has been detected in small quantities in several non-neural tissues, including corneal epithelium and hair follicles at the base of the neck, although the replication of rabies virus is not usually pronounced in nonneural tissue other than the salivary glands.

In all mammalian species the host is not infectious for most of the incubation period. Rabies infection is fatal in all species and no species is known to have a carrier state where virus is shed in the absence of clinical signs or imminent clinical signs. Exceptional and rare cases of human survivors have been recorded in a handful of cases where the patients did receive some prophylaxis but had severe residual neurological sequelae. To date only one case of a human survivor has been recorded in a patient who did not have any history of prophylaxis. The reason for the patient's recovery is still being investigated and disputed.¹⁸³

Immunity

The immune mechanism by which rabies virus is cleared from the host is not well understood. Protective immunity against rabies involves both B-cell (humoral) and various pathways of the T-cell response.²⁸ The effective humoral response is directed only against the glycoprotein envelope of the virus. Other proteins do not play any role in generating neutralising antibodies. Cytotoxic T-cell responses are directed against the glycoprotein, nucleoprotein and phosphoprotein components of the virus. Where the host has been successfully vaccinated, virions within a wound will be cleared mainly by the humoral immune system through neutralisation before they gain entry into the nervous system.

Once inside the neurons, virions are inaccessible to this immune pathway. This is the main reason for urgent initiation of post-exposure vaccination and passive immunoglobulin treatment. Additional cytolytic immune mechanisms may operate against intracellular virus. This may be the cause of the characteristic paralytic signs seen when rabid animals are improperly vaccinated. Inoculation of rabies virus-containing saliva into a wound does not normally induce a detectable immune response.

Animal and human rabies vaccines consist of inactivated whole-virus antigens grown on a cell culture or neural tissue substrate and, in the case of more modern cell-culture vaccines, partially purified to remove unnecessary proteins. Generally, veterinary pre-exposure vaccination, while human vaccines, which are considerably more expensive to produce, are used post-exposure. Pre-exposure vaccination may be recommended in people at high risk. There are no records of human rabies cases that have occurred in people fully vaccinated according to World Health Organisation (WHO) recommendations.

Post-exposure prophylaxis of humans, using vaccine and immunoglobulin according to WHO recommendations (page 39, table 10 and Fig 7. pg 41 or Appendix 2), provides rapid and effective protection if administered soon after exposure. The most frequent causes of failure of post-exposure prophylaxis are delays in administering the first vaccine dose or immunoglobulin, failure to complete the vaccine course and failure of correct wound management. Infiltration of the wound with immunoglobulin does not interfere with stimulation of the immune system by vaccine, which is administered at a site distant from the wound.

Rabies vaccine strains in current use protect against many, but not all, lyssavirus genotypes.¹⁸¹ Experimental models predict that vaccines based on these current vaccines strains will protect against so-called phylogroup 1 lyssavirus (including rabies, Duvenhage, European bat lyssa- 1 and 2 and Australian bat lyssaviruses), but not viruses belonging to phylogroup 2 (Lagos and Mokola viruses).^{29, 180-181} Further evidence for the lack of protection against Mokola as well as Lagos bat virus are the discovery of infections in vaccinated cats and dogs.^{17, 185}

RABIES IN ANIMALS

Species involved

A diagrammatic representation of the distribution of the main reservoirs of rabies in South Africa is provided in Fig. 3. The map is an approximation and there will be areas where considerable overlap occurs. The canid rabies virus biotype circulates predominantly in the areas indicated as endemic for dog, black-backed jackal and bat-eared fox rabies. Endemicity changes constantly and the domestic dog, which is dependent on humans for its existence, may be transported very rapidly over long distances.^{21,30} Future outbreaks of canine rabies in heavily populated, canine rabies-free areas of South Africa, are inevitable unless high levels of dog vaccination are achieved and maintained. This was demonstrated with the re-emergence and outbreak of rabies in the Limpopo Province in 2005.¹⁸⁴



Plate 4: The bat-eared fox is an important vector in the arid regions of South Africa

Rabies infection is fatal in all species and no species has a carrier state where virus is shed in the absence of clinical signs or imminent clinical signs

A list of species confirmed rabid by various South African laboratories over the period 1928 to 2006, is provided in Table 2. The list is not exhaustive and additional species will undoubtedly be included in future. To date, about 37% of all animal rabies cases have been dogs (67% from KwaZulu-Natal). Yellow mongooses have contributed 17% of the total but most of the 1 310 unspecified mongooses were certainly also *Cynictis penicillata*. The mongoose grouping (including suricates) contributed more than 27% of the total rabies cases. Dogs and mongooses therefore represent 64% of total cases. Species usually regarded as dead-end hosts (cattle, sheep, goats, horses and pigs) contributed 22% of the total.

Apart from the large-scale kudu outbreak in Namibia rabies has rarely been diagnosed in the large game reserves of southern Africa. Except for very rare intrusions of rabid domestic dogs from Mozambique into the Kruger Park (KNP) and KwaZuluNatal game reserves have until recently remained rabies-free [Onderstepoort Veterinary Institute (OVI) and Allerton Veterinary Laboratory unpublished laboratory records]. Rabies was confirmed in a jackal in greater KNP in November 2006 following a increase of canine rabies in the Limpopo Province (R. Bengis—personal communication). Small outbreaks have occurred in other game reserves.³¹

The geographical location of all animal rabies cases diagnosed over the five year period, 2002 to 2006-update, is displayed in Fig. 4. Illustrations of some of the wild animal species most frequently diagnosed rabid since 1990 are found in Plates 5 and 6.

Rabies distribution according to species

From the Directorate Animal Health Disease Database (outbreaks reported 1993 to 2008)

Legend

Number of outbreaks 1993 to 2008

Canine



Yellow Mongoose



Jackal



Bat Ear Fox



Provinces

Map Produced by:
Dr H. Piensaar
Sub-Directorate: Epidemiology
Directorate: Animal Health
23/09/2009

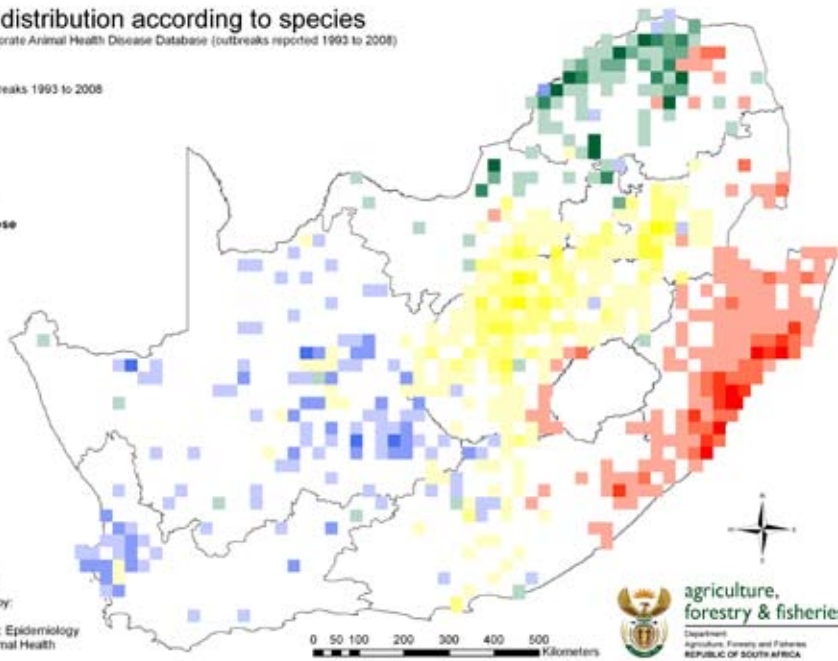


Fig. 3: The distribution of rabies endemicity by major vectors in South Africa

TABLE 2: Rabies cases diagnosed in South Africa, 1928 to 2006

Animal		1928–1991	1992–2000	2001–2006	Total
Domestic					
Dogs	<i>Canis familiaris</i>	3322	2433	2308	8063
Cats	<i>Felis domesticus</i>	437	146	104	687
Cattle	<i>Bos species</i>	2211	818	631	3660
Sheep	<i>Aries ovis</i>	119	39	36	194
Goats	<i>Capra hirsutus</i>	60	74	80	214
Horses and donkeys	<i>Equus caballus, Eq. asinus</i>	53	28	31	112
Pigs	<i>Suis scrofula</i>	25	11	6	42
Guinea pigs	<i>Cavia porcellus</i>	1	0	0	1
Total domestic		6228	3549	3196	12973
Wild					
Yellow mongoose	<i>Cynictis penicillata</i>	2034	553	313	2900
Slender mongoose	<i>Galerella sanguinea</i>	16	46	34	96
Small grey mongoose	<i>Galerella pulverulenta</i>	38	13	9	60
Large grey mongoose	<i>Herpestes ichneumon</i>	0	1	0	1
Banded mongoose	<i>Mungos mungo</i>	3	2	0	5
Water mongoose	<i>Atilax paludinosus</i>	11	17	6	34
Selous mongoose	<i>Paracynictis selousi</i>	1	0	1	2
Dwarf mongoose	<i>Helogale parvula</i>	1	0	0	1
White-tailed mongoose	<i>Ichneumia albicauda</i>	2	0	1	3

Wild (continued)		1928–1991	1992–2000	2001–2006	Total
Suricate	<i>Suricata suricatta</i>	112	86	24	222
Mongoose species		2218	718	388	3324
Civet	<i>Civettictis civetta</i>	3	3	3	9
Small-spotted genet	<i>Genetta genetta</i>	167	25	7	199
Lion	<i>Panthera leo</i>	0	1	0	1
African wildcat	<i>Felis lybica</i>	13	24	14	51
Caracal	<i>Felis caracal</i>	14	3	5	22
Serval	<i>Felis serval</i>	0	3	0	3
Small-spotted cat	<i>Felis nigripes</i>	3	2	2	7
Felid species		200	61	31	292
Honey badger	<i>Mellivora capensis</i>	18	9	2	29
Striped polecat	<i>Ictonyx striatus</i>	66	5	1	72
Striped weasel	<i>Poecilogale albinucha</i>	1	1	0	2
Black-backed jackal	<i>Canis mesomelas</i>	206	185	74	465
Bat-eared fox	<i>Otocyon megalotis</i>	263	160	88	511
Wild dog	<i>Lycaon pictus</i>	0	7	0	7
Cape fox	<i>Vulpes chama</i>	7	11	5	23
Aardwolf	<i>Proteles cristatus</i>	22	31	12	65
Brown hyaena	<i>Hyaena brunnea</i>	1	0	0	1
Spotted hyaena	<i>Crocuta crocuta</i>	1	0	2	3
Ground squirrel	<i>Xerus inauris</i>	32	11	6	49
Tree squirrel	<i>Paraxerus cepapi</i>	1	1	0	2
Greater cane rat	<i>Thryonomys swinderianus</i>	2	0	0	2
Cape hyrax	<i>Procavia capensis</i>	8	3	1	12
Chacma baboon	<i>Papio ursinus</i>	1	0	0	1
Warthog	<i>Phacochoerus aethiopicus</i>	1	0	0	1
Impala	<i>Aepyceros melampus</i>	0	1	0	1
Duiker	<i>Sylvicapra grimmia</i>	17	3	2	22
Steenbok	<i>Raphicerus campestris</i>	4	0	0	4
Kudu	<i>Tragelaphus strepsiceros</i>	3	4	1	8
Eland	<i>Taurotragus oryx</i>	0	3	0	3
Blesbok	<i>Damaliscus dorcas phillipsi</i>	1	0	0	1
Bushbok	<i>Tragelaphus scriptus</i>	0	1	0	1
Reedbuck	<i>Redunca arundinum</i>	1	0	0	1
Springbuck	<i>Antidorcus marsupialis</i>	3	0	0	3
Burchell's zebra	<i>Equus burchelli</i>	1	1	2	4
Herbivore species		6	0	0	6
Scrub hare	<i>Lepus saxatilis</i>	1	0	0	1
Unknown species		34	2	0	36
Total wild		3119	1218	615	4952
Total animals		9347	4767	3813	17925

The present areas of canine rabies endemicity will expand rapidly, unless high levels of dog vaccination are achieved and maintained

Note:

- A total of 17 bats, believed to have been infected with rabies-related viruses, have been omitted from this table
- A number of the cats listed are known to have been infected with Mokola virus (rabies-related virus)
- Most of the “Mongoose species” are believed to have been yellow mongoose

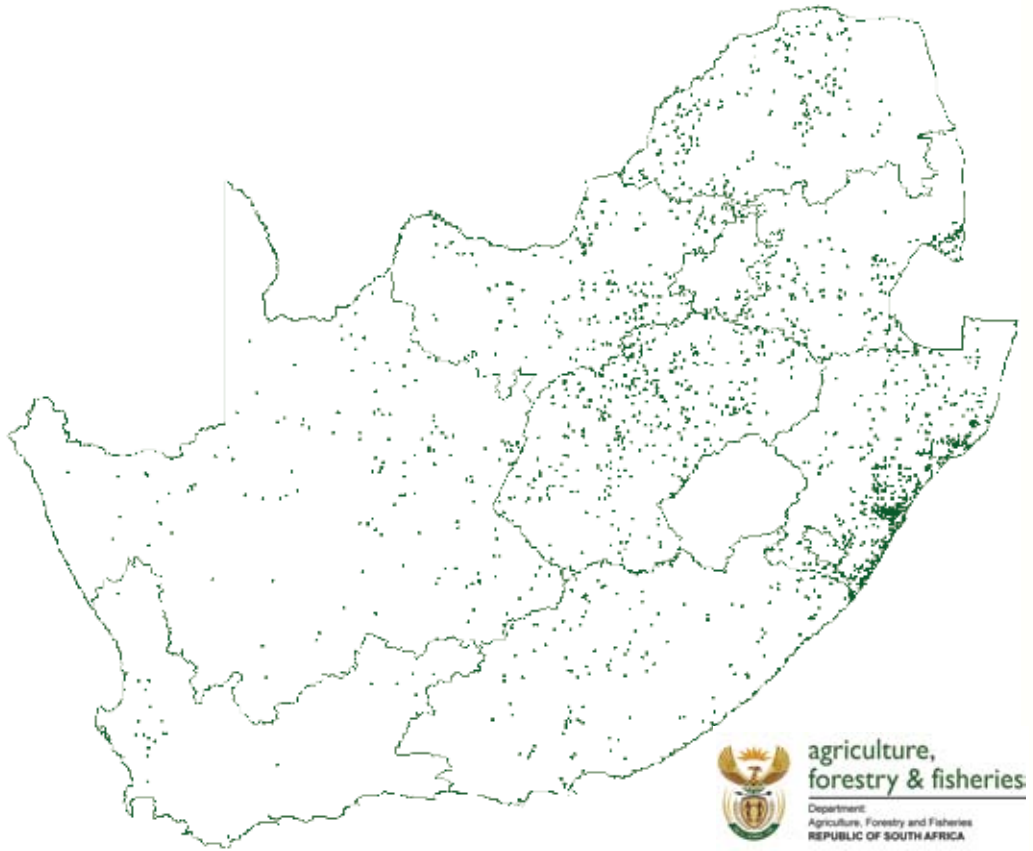


Fig. 4: Geographical locations of reported animal rabies outbreaks over the five year period, 2002 to 2006



Yellow mongoose
Cynictis penicillata



Slender mongoose
Galerella sanguinea



Black-backed jackal
Canis mesomelas

Plate 5: Wild mammal species associated with rabies in South Africa



Bat-eared fox
Otocyon megalotis



Small spotted genet
Genetta genetta



Suricate
Suricata suricatta



Small grey mongoose
Galerella pulverulenta



Striped polecat
Ictonyx striatus



Aardwolf
Proteles cristatus



Ground squirrel
Xerus Inauris



African wild cat
Felis lybica



Badger
Mellivora capensis



Cape fox
Vulpes chama



Water mongoose
Atilax paludinosus

Plate 6: Wild mammal species associated with rabies in South Africa

Transmission and epidemiology

An understanding of the importance of the virus-host-environment relationship is crucial to understanding the complex epidemiology of animal rabies.²⁰ With recent developments in monoclonal antibody technology and gene sequencing, it is possible to demonstrate that distinct variants of rabies viruses (Lyssavirus type 1) have become adapted to specific hosts. The South African canid strain appears to be homogeneous whereas there are at least four or five mongoose strains. Within the mongoose strains, an association has been shown with different yellow mongoose populations occurring in geographically distinct areas.^{18,32,163} The underlying causes of rabies-virus-host preference and the factors that determine the propensity of a rabies virus strain to spread, or become compartmentalised, have not been elucidated. Rabies does not appear to have an extended asymptomatic carrier phase and a symptomless carrier animal, which sheds rabies virus but does not succumb to the disease, has not been demonstrated in South Africa. Animals infected with rabies virus succumb to the disease.

More than 300 animal rabies (Lyssavirus type 1) isolates from KwaZulu-Natal have been typed using monoclonal antibodies and these have all proved to be canid strain.²¹ This finding clearly implicates the domestic dog as the reservoir species in that province and is justification for the veterinary authorities' policy of intensive dog vaccination. A good knowledge of local dog ecology (dog numbers, turnover rates, reasons for ownership, other diseases, housing) is crucial when planning control measures. Feral dogs do not appear to be an important factor in KwaZulu-Natal and therefore owners' management of their dogs should not be overlooked.

Dog rabies is almost exclusively endemic in developing countries where control measures are difficult to apply and education of the public is complicated by competing priorities. Dog rabies has often erroneously been referred to as "urban" rabies but the disease is clearly a rural problem in many parts of the Eastern Cape, Mpumalanga and KwaZulu-Natal. The term "urban" may have originated with the belief that urban domestic dogs maintained a rabies

cycle that originated from sylvatic mongoose rabies spreading to dogs in South Africa.²⁰

The identification of different rabies variants by means of monoclonal antibody typing and gene sequencing has put this postulate to rest.

Canine rabies is currently endemic in the north-eastern regions of the Eastern Cape, the entire KwaZulu-Natal, and the eastern and south-eastern areas of Mpumalanga adjoining Swaziland.^{21,30} Within these regions, prevalence appears to be highest in areas with the highest human densities. Human migration has increased considerably during the past decade and it may only be a matter of time before canine rabies makes its presence felt in other densely populated areas of the country.

During the past 30 years, the canid strain of rabies virus has accounted for most black-backed jackal rabies cases in the Limpopo Province and bat-eared fox rabies cases in the Northern Cape, Free State and Eastern Cape. A rabid black-backed jackal, some 20 km from Soweto, yielded the canid strain in 1995. Why large-scale spreading to the local dog populations did not occur, remains a mystery.

Humans, cattle and other domestic animals are the main victims of canid rabies in dog rabies-endemic regions.^{21,30} In the Limpopo and North West Provinces, cattle are most frequently affected by outbreaks in black-backed jackal. Epidemics appear to occur in cycles of eight to 10 years, and two specific epidemics from 1974 to 1980 and 1988 to 1996 had significant economic implications. During the former more than 1 000 cattle succumbed to clinical rabies on 93 farms (H. van de Pypekamp, personal communication). Rabies in jackal was controlled by poison baits until the 1980s. This method proved unsuccessful and often led to the death of nontarget species. It has since been replaced by mass vaccination of livestock in endemic areas with far better results. Unlike dog rabies, sylvatic rabies may be influenced to a far greater extent by seasonal availability of water and food. Competition between species during the mating season and dispersal of progeny seeking new territories, appear to be important

Humans, cattle and other domestic animals are the main victims of canine rabies in dog rabies endemic regions

explanatory factors.¹⁸ The increased prevalence of the disease in black-backed jackal in areas of the Limpopo Province from July to November over a number of years coincided with mating and whelping in these animals.^{33,34}

Rabies appears to spread fairly well within bat-eared fox populations, yet transmission of infections to other species is relatively rare. The underlying reasons for this are still to be elucidated. Population dynamics (including population turnover) and the distribution of susceptible animals are extremely important factors determining the prevalence of rabies in other species, and the bat-eared fox is no exception.

The most important maintenance host of mongoose rabies is the yellow mongoose, *Cynictis penicillata*, a diurnal animal that lives in colonies of 10 or more individuals. The disease has been endemic in yellow mongoose populations for decades and possibly centuries. Attempts by veterinary authorities to control the disease by depopulation, for example by gassing burrows and trapping, have only had a transient effect. These measures may ultimately have accelerated the spread of the disease by increasing the territories of yellow mongoose colonies with concomitant increased movement. Spreading infection to suricates, which are migratory herpestids living in groups of up to 30 individuals, and ground-squirrel populations are fairly common, because these species often share warrens or live in close proximity to yellow mongoose colonies.

Humans and domestic animals such as sheep, cattle and dogs have been infected and succumbed to mongoose rabies virus but are regarded as dead-end hosts because spread within these species is rare.

Clinical signs

Apart from behavioural changes, there are no definitive, species specific clinical signs of rabies.^{24,35} Although certain clinical signs are more frequent than others, even the most experienced diagnostician may make an incorrect diagnosis when presented with an unusual case. Rabies can mimic many other diseases but it always has a neurological component.

The most important maintenance host of mongoose rabies is the yellow mongoose

Histories, submitted to diagnostic laboratories have often included the words: “typical rabies” or “typical dumb rabies” or “typical furious rabies” without any further elaboration of what the sender regarded as “typical”.^{21,30} Some early workers in the rabies field appeared to agree on a typical presentation of a rabid dog and Baer cites Philumenus, Ibn Sina and Galen (130 AD) as all agreeing that: “If you hear that the dog is wasted in the body, dry, red

in the eyes, tail hanging limp, its tongue hanging out and discoloured, bumping into people it meets, irrationally running and stopping, biting with furious rage people it has never met before, then you may be sure the dog is rabid”.³⁶



Plate 7: Aggressive behaviour in unusual circumstances is well documented in domestic and wild animals infected with rabies virus

Because rabies affects the central nervous system, it is nearly always associated with behavioural changes that may manifest in many different ways. Classically, rabies has been described as having a prodromal phase followed by either an excitive furious form, or a paralytic dumb form.³⁷

The veterinarian is, however, rarely afforded the opportunity to observe an animal throughout the clinical course of disease and diagnosis is often made after minimal observation, especially in endemic areas

where rabies awareness is heightened. For this reason, a list of clinical signs in rabid animals (in no particular order) during various stages in the course of the disease is provided here.^{18,24,37} Some of the signs, such as a change in disposition, may only be noticed after close observation by owners or people closely associated with the particular animal.



Plate 8: Paralytic rabies in a dog that is salivating profusely

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, a febrile reaction, uncoordinated actions and progressive paralysis, dilated pupils, irritability, photophobia, infliction of self-injury, convulsions, and muscle spasms.
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, butting 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 pen, hypersexual behaviour, aggression, biting, and may kill offspring.
Wild animals:	Often lose fear of humans.
	Yellow mongooses generally demonstrate tame behaviour, but some are very aggressive.
	Jackal are usually aggressive, and lose fear of humans.
	Wild cats display similar behaviour to domestic cats. Badgers are usually vicious and fierce.
	Kudu salivate profusely, may be paralysed, docile, tame, even entering houses. Duiker are sometimes very aggressive.

Plate 9: Behavioural changes are common in wild animals, which may appear to become “tame”. This rabid kudu has entered the kitchen of a Namibian farmhouse



Plate 10: Knuckling fetlocks and hind-quarter paralysis in a bovine

Rabies can mimic many other diseases but it always has a neurological component, with behavioural changes



Plate 11: Hind-quarter paralysis in a calf



Plate 12: Inquisitive cattle are often bitten by animals which exhibit unusual behaviour. Many cattle may be bitten at the same time in these circumstances



Plate 15: Salivation, which is particularly acute in terminal disease, persistent bellowing and wind-sucking in a bovine



Plate 14: Continuous bellowing is well documented in cattle



Plate 13: Rabid cattle may become very thirsty and attempt to drink but are unable to swallow. Sick animals often loiter at watering points

Animals displaying signs of neurological disease, as well as all stray and wild animals suspected of exposing humans to rabies infection, should be euthanised for laboratory confirmation

An analysis of the unsolicited histories submitted on 2 743 rabies specimen submission forms (2 465 confirmed dogs, 169 cattle, 59 cats, 37 goats and 13 horses) to Allerton Provincial Veterinary Laboratory in KwaZulu-Natal over approximately 12 years, is provided in Tables 3 to 7.

TABLE 3: Clinical signs reported in histories submitted for 2 465 confirmed rabies cases in dogs from September 1987 to December 1999

Clinical sign	No.	%
Aggression	1 095	44
Bit human, other animal	628	26
Behavioural changes	559	23
Salivation	541	22
Slack or dropped jaw, jaw paralysis	418	17
Incoordination, ataxia	392	16
Biting foreign objects	353	14
Abnormal sounds, howling	333	14
Not eating	236	10
Paralysis, paresis	183	7
“Nervy”, agitated, sensitive to noise/ light	153	6
Dumb, dull, lethargic	146	6
Exhausted, collapsed, emaciated	117	5
Central nervous system disorder, confused, “crazy”	110	5
Vacant expression, fixed stare	108	4
Running in circles, running aimlessly	95	4
Muscle twinges, spasms	91	4
Convulsions, seizures	87	4
Tongue hanging out	60	2
Pyrexia	49	2
Difficulty in swallowing	46	2
Depression	39	2
“Fly snapping”	38	1
“Bone in the throat”	35	1
Disappeared for a few days	31	1
Vomiting	27	1
Hydrophobia	20	1
“Chewing gum fit”	18	1
Blind, appeared to be blind	18	1
Self-mutilation, biting itself	16	1
Hiding away	13	1
Diarrhoea	12	119

TABLE 4: Clinical signs reported in histories submitted for 169 confirmed rabies cases in cattle from September 1987 to December 1999

Clinical sign	No.	%
Abnormal sounds, bellowing	120	71
Salivation	94	56
Aggression	75	44
Behavioural changes	43	25
Chasing chickens, cattle and other animals	26	15
Incoordination, ataxia	23	14
Not eating	22	13
Paralysis, paresis	10	6
Exhausted, collapsed, emaciated	9	5
Vacant expression, fixed stare	9	5
“Nervy”, agitated, sensitive to noise/light	7	4
Hypersexual behaviour	6	4
Convulsions, seizures	6	4
Bit human, other animal	6	4
Central nervous system disorder, confused, “crazy”	5	3
Biting foreign objects	5	3
Running in circles, running aimlessly	5	3
Walking in circles	4	2
Muscle twinges, spasms	4	2
Disappeared for a few days	3	2
Knuckling of fetlocks	3	2
Dumb, dull, lethargic	3	2
Restless	3	2
Difficulty in swallowing	3	2
Pyrexia	2	1
Hydrophobia	2	1
Slack or dropped jaw, jaw paralysis	2	1
Tongue hanging out	2	1
“Bone in the throat”	1	1
Depression	1	1
Unusually tame	1	1
Blind, appeared to be blind	1	1
Vomiting	1	1

TABLE 5: Clinical signs reported in histories submitted for 59 confirmed rabies cases in cats from September 1987 to December 1999

Clinical sign	No.	%
Bit human, other animal	28	48
Aggression	25	42
Behavioural changes	16	27
Incoordination, ataxia	7	12
Biting foreign objects	5	9
Salivation	4	7
Slack or dropped jaw, jaw paralysis	4	7
“Nervy”, agitated, sensitive to noise/light	3	5
Disappeared for a few days	3	5
Abnormal vocalisation	3	5
Not eating	3	5
Convulsions, seizures	3	5
Exhausted, collapsed, emaciated	2	3
Self-mutilation, biting itself	1	2
Paralysis, paresis	1	2
Pyrexia	1	2
Restless	1	2
Dumb, dull, lethargic	1	2
Depression	1	2
Unusually tame	1	2
Walking in circles	1	2
Difficulty in swallowing	1	2

TABLE 6: Clinical signs reported in histories submitted for 37 confirmed rabies cases in goats from September 1987 to December 1999

Clinical sign	No.	%
Aggression	20	54
Behavioural changes	13	35
Difficulty in swallowing	11	30
Biting foreign objects	11	30
Abnormal vocalisation	11	30
Chasing chickens, cattle, other animals	10	27
Salivation	6	16
Bit human, other animal	5	14
Paralysis, paresis	4	11
Central nervous system disorder, confused, "crazy"	3	8
Not eating	3	8
"Nervy", agitated, sensitive to noise/light	2	5
Self-mutilation, biting itself	2	5
Knuckling of fetlocks	2	5
Muscle twinges, spasms	1	3
Hiding away	1	3
"Chewing gum fit"	1	3
Hypersexual behaviour	1	3
Incoordination, ataxia	1	3

TABLE 7: Clinical signs reported in histories submitted for 13 confirmed rabies cases in horses from September 1987 to December 1999

Clinical sign	No.	%
Aggression	8	62
Behavioural changes	6	46
Self-mutilation, biting itself	5	38
Biting foreign objects	4	31
Incoordination, ataxia	3	23
Bit human, other animal	3	23
Central nervous system disorder, confused, "crazy"	2	15
Chasing other animals	2	15
Muscle twinges, spasms	1	7
Pyrexia	1	7
Running in circles, running aimlessly	1	7
Slack or dropped jaw, jaw paralysis	1	7

Diagnosis

Confirmation of a clinical diagnosis of rabies cannot be made by gross pathology or histology. Specific tests must demonstrate the presence of rabies antigen. Animals displaying signs of neurological disease, and all stray and wild animals suspected of exposing humans to rabies infection, should be euthanised for examination. The Directorate Veterinary Services may hold suspected cats and dogs in quarantine for observation by a veterinarian for a period of at least 10 days.³⁸ Animals displaying signs of illness during the period of observation are euthanased for laboratory examination. A vaccination history may be of some assistance during the assessment but greater reliance should be placed on the animal's clinical picture. Although the inactivated veterinary vaccines used in South Africa are known to be extremely effective for periods exceeding three years following vaccination, there are compelling reasons for avoiding undue reliance on vaccination history alone.¹⁸

These include:

- the incorrect vaccine may have been administered
- the incorrect dosage and route may have been used
- the vaccine might have passed its expiry date
- the vaccine may have been incorrectly handled or stored
- the animal may have been misidentified
- vaccination may have been performed after infection had already occurred
- the animal may have been immuno-suppressed
- the animal may have been diseased or in poor condition when vaccinated
- the animal may have been very young at vaccination and not boosted at three months.

In addition, rabies has rarely been recorded in fully immunized animals.

Laboratory diagnosis

Rabies tests on domestic and wild animal specimens are performed at approved laboratories. Presently the Rabies Unit at the Agriculture Research Council-Onderstepoort Veterinary Institute (ARC-OVI) near Pretoria, and the Allerton Provincial Veterinary Laboratory (APVL), Pietermaritzburg are the approved laboratories in South Africa. The Rabies Unit at OVI is also recognized as the OIE Regional Rabies Reference Centre for Southern and Eastern Africa.

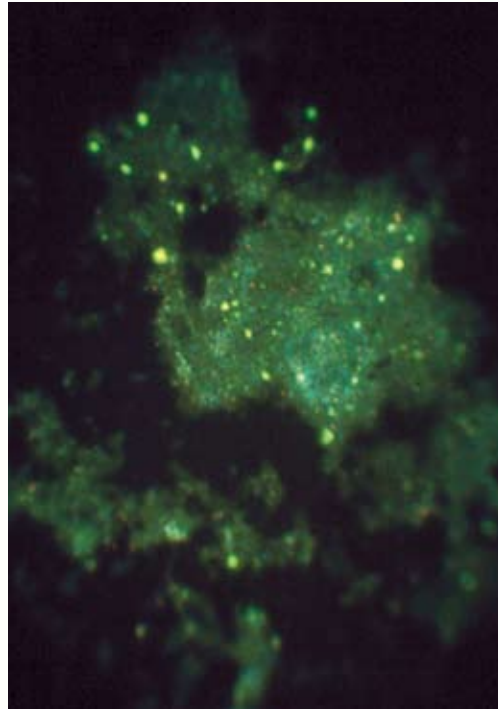


Plate 16: The fluorescent antibody test is used routinely to diagnose rabies in the brain tissue of animals and humans. Note the oval apple-green Negri bodies which are diagnostic of the disease

It is essential that a complete history of the animal involved and the circumstances surrounding the collection of the specimen be supplied to the laboratory. Specimen forms may be obtained from the OVI or APVL. The specimen form appearing as Fig. 6, page 31, may be reproduced and used for submission to either laboratory. State veterinarians must also receive a copy of the completed specimen form when the animal's brain is sent to the laboratory. The state veterinarian must send a copy of this form to the provincial Department of Health for the attention of the section responsible for communicable

It is essential that a complete history of the animal involved and the circumstances surrounding the collection of the specimen be supplied to the laboratory

disease control if they suspect that the animal had rabies or a positive test result is received.

The fluorescent antibody test (FAT) is the standard diagnostic test currently used in South Africa, and elsewhere.¹⁶⁴ The presence of rabies virus antigen is demonstrated in brain smears by means of immunofluorescence using antirabies fluorescein conjugate. The FAT is more than 99% reliable in experienced hands. The conjugate produced by the Rabies Unit at ARC-OVI will also detect rabies-related virus antigen. (Personal communication, Claude Sabeta). Commercial conjugates are also available.

Supplementary tests used include cell culture, mouse inoculation, the polymerase chain reaction and immunohistological tests. Histopathology, which makes use of formalin-impregnated brain sections, is not always informative for rabies infection but may help to exclude conditions in the differential diagnosis of rabies.³⁹

The FAT can be completed within 2 hours of receiving suitable brain material and delays in obtaining laboratory results are usually due to transportation problems.^{21,30} Because post-exposure prophylaxis of humans should be instituted without delay, decisions on the correct course of action are usually taken before the results of veterinary diagnostic tests become available. However, the results of laboratory tests are used, in conjunction with the clinical history, to decide whether antirabies prophylaxis should be continued or discontinued.

Differential diagnosis

Rabies must be considered in the differential diagnosis of any suspected mammalian encephalitis. Various conditions that have been confused with rabies are listed in Table 8.^{18,40}

TABLE 8: Several conditions that may be clinically confused with animal rabies

Dogs	Cattle	Horses	Sheep	Cats
Diseases				
Distemper	Cerebral theileriosis	Equine encephalosis	Heartwater	Toxoplasmosis
Infectious canine hepatitis	Thrombotic meningoencephalitis (<i>Haemophilus somnus</i>)	Encephalomyelitis (equine herpesvirus 1)	Botulism	Meningitis/encephalitis
Meningitis/encephalitis	Cerebral babesiosis	Tetanus	Meningitis/encephalitis	
Cerebral babesiosis	Heartwater			
Cerebral cysticercosis (<i>Taenia solium</i>)	Sporadic bovine encephalomyelitis (<i>Chlamydia psittaci</i>)			
Toxoplasmosis	Botulism			
Tetanus	Meningitis/encephalitis			
Ehrlichiosis				
Other conditions				
Oesophageal obstruction	Oesophageal obstruction		Coenurus cerebralis (<i>Taenia multiceps</i>)	Traumatic accidents
Foreign objects lodged in mouth/throat	Cerebrocortical necrosis (thiamine deficiency)		Cerebrocortical necrosis (thiamine deficiency)	Maternal aggression
Brain tumours	Foreign objects lodged in mouth/throat		Brain abscesses	Inter-cat aggression
Maternal aggression	Brain abscesses			Brain tumours
Traumatic accidents	Epidural abscesses			
Oestrous behavioural changes	Brain tumours			
Mineral/ pesticide poisoning				
Diminazene	Lead	Pesticide poisoning	Urea	Organophosphate
Chlorinated hydrocarbon	Urea		Organophosphate	Chlorinated hydrocarbon
Strychnine	Organophosphate		Chlorinated hydrocarbon	Strychnine
Organophosphate	Chlorinated hydrocarbon			
Methaldehyde				
Plant poisoning				
	<i>Homeria</i> and <i>Moraea</i> spp. (tulip)	Seneciosis	<i>Homeria</i> and <i>Moraea</i> spp. (tulip)	
	<i>Pennisetum clandestinum</i> (kikuyu grass)	<i>Fusarium moniliforme</i> (leukoencephalomalacia)	<i>Cynanchum</i> spp. (monkey rope)	
	<i>Dipcadi glaucum</i> (wild onion)		<i>Diplodia maydis</i> (diplo-diosis)	
	<i>Diplodia maydis</i> (diplo-diosis)			
	<i>Albizia</i> spp.			
	<i>Cestrum</i> spp. (ink berry)			
	<i>Cynanchum</i> spp. (monkey rope)			
	<i>Matricaria nigellifolia</i> (stagger weed)			
	<i>Aspergillus clavatus</i> (mycotoxicosis)			



Plate 17: Terminal rabies can be confused with many other animal diseases, such as corridor disease, cerebral redwater and heartwater

Prevention of Rabies

Pre-exposure vaccination

A number of recently developed, highly-effective, thermostable, inactivated vaccines are available in South Africa for veterinary use. The duration of immunity conferred varies from one to three years. Most veterinary vaccines are only registered for use in specific species, for example dogs. Although there are no safety limitations to their use, their efficiency in other species, for example mongoose, is not guaranteed. All rabies vaccines registered for human and animal use must conform to established potency standards. A minimum antigenic potency of 2,5 IU per dose is mandatory.⁴¹

The vaccines may be used in young pups, but they must be boosted at three months of age and again within the following year. Revaccination must be carried out every three years thereafter. Cattle and sheep may be vaccinated annually or every two to

three years, depending on the vaccine manufacturer's instructions. Some farmers inoculate their herds every year in jackal and dog rabies endemic areas with these inexpensive vaccines as they consider this practice to be economically sound.

Following an outbreak in domestic livestock, vaccination of animals without visible bite wounds is strongly recommended. In cases where bite wounds are visible, or there is direct evidence that an animal was bitten, the animal should immediately be isolated and destroyed.

Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) of bite-contact unvaccinated carnivores, including dogs and cats, is not recommended in South Africa. Preliminary reports indicate that antibodies in the form of antirabies immunoglobulin (RIG) in combination with vaccine yielded poor results.⁴² The use of PEP in animals is not without risk and is not recommended for use in animals in South Africa.

Procedures to be followed when rabies is suspected in animals

Collection and dispatch of specimens

People responsible for collecting specimens must be vaccinated against rabies.

Animals should be euthanased without causing extensive damage to the brain. Protective clothing, which should include gloves, an overall, a plastic apron, gumboots and a visor, must be worn while removing the brain. Collection of specimens should occur in a dedicated postmortem room or in the field. It is advisable that a bucket and disinfectant be available for onsite cleaning. The minimum equipment required is a coarse-bladed saw, a knife, a scalpel, forceps, scissors and a spatula (Plate 18).

The skin should be divided in the mid-line and the skull split along the mid-line into two halves using a coarse-bladed saw (Plates 23–27). This divides the brain as well. The brain should then be carefully removed with the aid of the scissors and forceps. In large animals sawing across just in front of the base of the horns is useful for opening the skull (Plates 19–20).

All bovines with neurological symptoms that test negative for rabies are tested for bovine spongiform encephalopathy (BSE). Although BSE has never been diagnosed in South Africa, ongoing surveillance is essential to prove that the country remains disease free.

It is preferable to submit the entire brain. If this is not possible, submit one half of the brain and brainstem or alternatively, cut off most of the cerebrum and submit only the brainstem, cerebellum, medulla

oblongata and one cubic centimetre section from each of the cranial, lateral and caudal cerebrum. Brain samples should be submitted in 50% glycerol-saline in a leak-proof bottle. If preservative is not available, brains may be stored in empty bottles and submitted without delay on ice by courier service, or hand-delivered to the laboratory.

Rabies can be diagnosed from any part of the brain, the spinal cord, peripheral nerves and salivary glands. However, the test is most reliable using the thalamus, pons medulla oblongata, hippocampus and cerebellum (Plates 21–22).¹⁶⁸

The specimen bottles should each be enclosed separately in a plastic packet and then tied off together in another plastic packet. The parcel containing the bottles should contain copious quantities of shredded paper, or other absorbent material, to absorb any fluid that may leak from the bottles (Plate 28). Accurate documentation on the correct submission form and a complete case history are extremely important for guiding laboratory interpretation, follow-up actions and control measures. All specimens submitted to a laboratory should be boldly marked as “**Suspected rabies**”.

The head and carcass should be burnt or buried in a plastic bag. After removal of a brain all equipment and work surfaces must be thoroughly disinfected and cleaned before removing the brain of another animal. All disposable clothing should be incinerated while reusable protective wear must be disinfected or autoclaved before washing.

Brain samples should be submitted in 50% glycerol-saline



Plate 18: Basic equipment needed for removing a brain



Plate 19: In large animals saw across just in front of the base of the horns



Plate 20: This incision exposes the brain

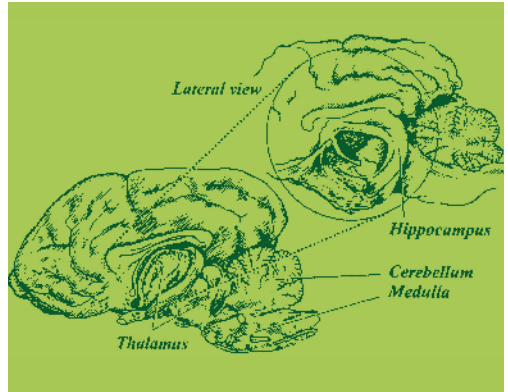


Plate 21: Schematic presentation of the anatomy of the brain

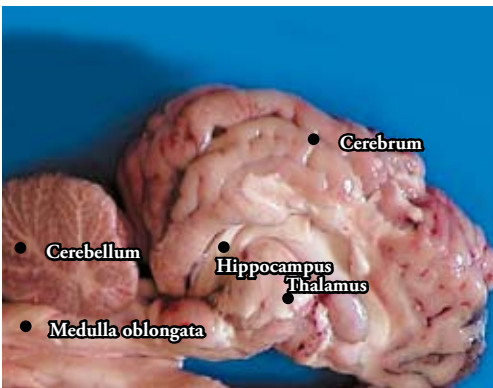


Plate 22: Lateral view of the anatomy of the brain



Plate 23: Alternative approach by longitudinal section



Plate 24: The skin is cut down the mid-line to expose the skull. Note the protective gloves being worn by the person removing the dog's brain



Plate 25: The skull is being sawn along the mid-line. Note the protective gloves, visors and overalls being worn by both operators



Plate 26: The skull is opened and the brain is carefully removed using a scissors and forceps



Plate 27: An animal brain which has been split longitudinally in half



Plate 28: Brain specimens secured in screw cap plastic jar, sealed in two plastic bags, surrounded by sufficient absorbent material and packed in a firm cardboard box



Plate 29: Brain removal during human autopsy. Note the protective equipment being worn by the operators

Reporting procedure and documentation

The results of laboratory tests for rabies must be disseminated as indicated in the diagram below (Fig. 5). All results should preferably be faxed but where

this is not possible, results must be communicated by phone and an official letter posted. State veterinarians and the provincial veterinary director will appoint a responsible clerk to maintain a register.

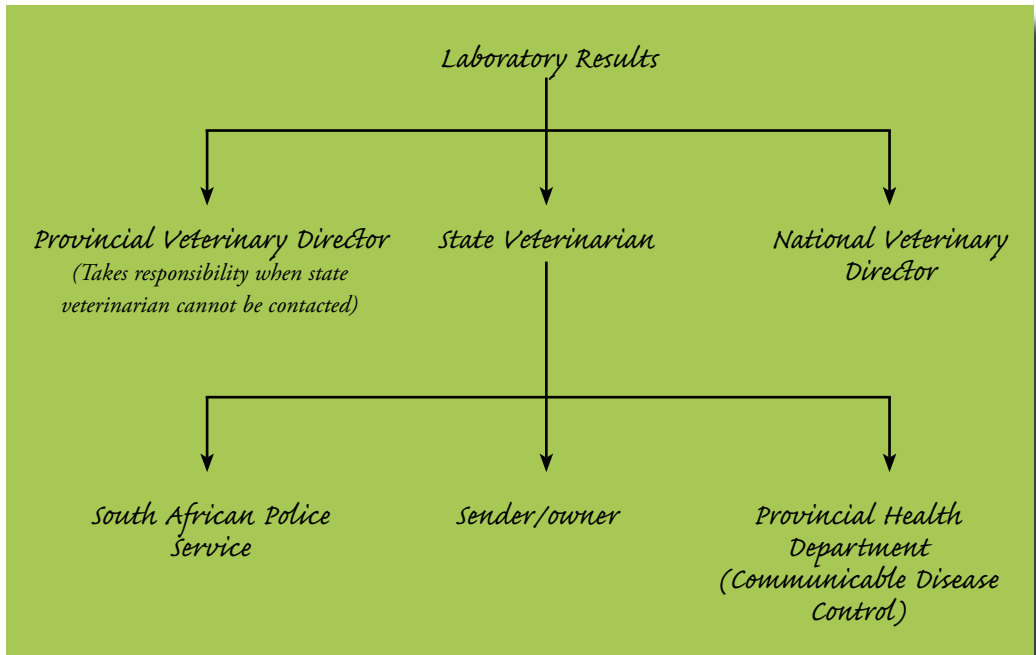


Fig. 5: Distribution of laboratory results

DIRECTORATE VETERINARY SERVICES RABIES SPECIMEN SUBMISSION FORM

Please send a copy of this form to your local state veterinarian
Complete all sections thoroughly and carefully. If insufficient space, write on reverse Specimens must be submitted on ice, or in glycerol-saline, in clearly labelled, leak-proof containers and not in formalin

SENDER: NAME <input style="width: 200px;" type="text"/>		SENDER'S REFERENCE <input style="width: 100px;" type="text"/>	
ADDRESS <input style="width: 500px;" type="text"/>			
<input style="width: 150px;" type="text"/>		PHONE CODE & NUMBER <input style="width: 100px;" type="text"/>	FAX <input style="width: 50px;" type="text"/>
OWNER: NAME <input style="width: 200px;" type="text"/>		PHONE NUMBER <input style="width: 100px;" type="text"/>	
ADDRESS <input style="width: 500px;" type="text"/>			
SPECIMEN ORIGIN: FARM NAME AND ADDRESS <input style="width: 450px;" type="text"/>			
<input style="width: 150px;" type="text"/>		FARM NUMBER <input style="width: 100px;" type="text"/>	GRID REFERENCE <input style="width: 50px;" type="text"/>
STATE VET. AREA <input style="width: 150px;" type="text"/>		MAGISTERIAL DISTRICT <input style="width: 100px;" type="text"/>	
SPECIES: COMMON NAME <input style="width: 300px;" type="text"/>			AGE (IF DOG) <input style="width: 50px;" type="text"/>
SCIENTIFIC NAME: <input style="width: 500px;" type="text"/>			
CLINICAL SIGNS AND HISTORY: DATE OF DEATH <input style="width: 100px;" type="text"/>		DURATION OF SIGNS <input style="width: 100px;" type="text"/>	
CLINICAL SIGNS AND HISTORY <input style="width: 100%; height: 100%;" type="text"/>			
VACCINATION HISTORY: (If known) DATES OF VACCINATIONS <input style="width: 300px;" type="text"/>			
Mark with "X" if: NOT VACCINATED <input type="checkbox"/> VACCINATION UNCERTAIN <input type="checkbox"/> VACCINATED BUT DATE UNCERTAIN <input type="checkbox"/>			
HUMAN CONTACTS:		NUMBER OF CONTACTS	
NONE <input type="checkbox"/>	DON'T KNOW <input type="checkbox"/>	BITE	SALIVA
		HANDLING	OTHER (SPECIFY)
NAME OF CONTACT		ADDRESS	
<input style="width: 150px;" type="text"/>		<input style="width: 200px;" type="text"/>	
<input style="width: 150px;" type="text"/>		<input style="width: 200px;" type="text"/>	
<input style="width: 150px;" type="text"/>		<input style="width: 200px;" type="text"/>	
RESPONSIBLE PERSON: (PRINT) <input style="width: 150px;" type="text"/>		RANK/OCCUPATION <input style="width: 100px;" type="text"/>	
DATE: <input style="width: 100px;" type="text"/>		SIGNATURE: _____	
OFFICIAL	RABIES # <input style="width: 50px;" type="text"/>	LAB # <input style="width: 50px;" type="text"/>	DATED REC'D <input style="width: 50px;" type="text"/>
			TIME REC'D <input style="width: 50px;" type="text"/>
DATE OF TEST <input style="width: 50px;" type="text"/>	TIME OF TEST <input style="width: 50px;" type="text"/>	DATE FAXED <input style="width: 50px;" type="text"/>	TIME FAXED <input style="width: 50px;" type="text"/>
COMMENT:			FAT RESULT <input style="width: 50px;" type="text"/>

Fig. 6: Rabies specimen submission form

RABIES IN HUMANS

Epidemiology of human rabies

Rabies is an ongoing scourge exacting an unnecessarily large toll on human life. The World Health Organization estimates about 55 000 human deaths in canine rabies endemic areas (31 000 in Asian countries and 24 000 in African countries) annually.^{43, 44, 45, 159} Rabies virus is transmitted via the saliva of infected animals and has the highest case fatality rate of any known human infection if the disease has manifested. Once the virus has entered the central nervous system of the host, the resulting encephalomyelitis is fatal. Fortunately the availability of efficacious and safe vaccines and immunoglobulin has prevented many fatalities and almost 10 million people receive post-exposure prophylaxis annually after potential rabies exposure, mostly following dog bites.

Rabies and the developing world

Rabies remains endemic throughout the world except for certain Western European countries and a number of islands, but more than 99% of all human rabies deaths occur in the poorest developing countries.^{45,46,47} Recorded deaths in developing countries probably provide a gross underestimate of the true situation as these areas generally have notoriously poor notification systems. Reasons underlying the preponderance of rabies cases in poor countries are complex but include opposing needs and limited resources for veterinary control, the prohibitive cost of post-exposure vaccine and immunoglobulin, poorly informed communities, inadequately trained health and veterinary staff, and inaccessibility of health-care facilities.^{48,49,50}

Of considerable concern is the re-emerging status of rabies in Africa.^{51,173} This trend has been attributed to rapid population growth with parallel dog population growth directed by security concerns, for example a growth of 4,7% in the dog population in Zimbabwe between 1954 to 1986, mobility of human populations, particularly political refugees, high rates of urbanisation and a disintegration of veterinary rabies control.^{52,53,54} The latter is of particular importance as dog rabies vaccination is a more cost-effective measure for preventing human

rabies than reliance on post-exposure prophylaxis for dog-bite victims.⁵⁵

Distribution in South Africa

During the first half of the 20th century most human rabies cases in South Africa resulted from herpestid, particularly yellow mongoose, bites in the central plateau areas. However, following the introduction of canid virus into Limpopo Province in the late 1940s, and later into KwaZulu-Natal in 1961, dogs became the most important source of human infection. In recent years (Table 9) the vast majority of South African human rabies cases have followed bites from infected dogs in KwaZulu-Natal.^{56,57} An outbreak of rabies in dogs coincided with a dramatic increase in the number of human cases in the Limpopo Province in 2006.¹⁸⁴

Most victims have been children under the age of 10 years. Children are particularly vulnerable because of their height, inquisitive nature, interest in animals and inability to protect themselves. Surveillance of human rabies is poor in many parts of South Africa and it is likely that the situation may be worse than that reflected by official notifications. A careful history taken from a victim's family has demonstrated a high sensitivity for diagnosing rabies in other African settings and may prove a useful approach in areas suspected of having rabies cases that have not been notified.⁵⁸

Canine vaccine delivery targeted to highest risk populations and broad intersectoral collaboration are believed to have contributed to the marked reduction in human rabies in KwaZulu-Natal during the latter part of the 1990s.^{59,60}

Transmission to humans

Human rabies cases result from viral introduction through broken skin or mucosa through encounters with rabid animals, particularly bites but also scratches and nicks. Virus is usually present in the saliva of the affected animal during clinical disease but secretion may be intermittent. Experimental demonstration of virus in salivary glands or saliva several days before

TABLE 9: Laboratory-confirmed human rabies cases in South Africa, 1986 to 2007

Year	Kwa-Zulu-Natal	Eastern Cape	Mpumalanga	Northern Cape	Free State	North West	Limpopo Province	Western Cape	Gauteng	Total
1986	7	0	1	0	0	1	0	0	0	9
1987	16	1	0	1	0	0	0	0	0	18
1988	25	1	0	0	2	0	0	0	0	28
1989	10	0	0	0	0	0	0	0	0	10
1990	11	0	0	1	0	0	0	0	0	12
1991	20	0	0	0	0	0	0	0	0	20
1992	22	2	0	0	0	0	0	0	1	25
1993	21	2	0	0	1	0	0	0	0	24
1994	18	1	0	0	0	0	0	0	0	19
1995	29	0	0	0	0	0	0	0	0	29
1996	12	2	0	0	0	0	0	0	0	14
1997	3	2	0	0	0	1	0	0	0	6
1998	5	1	0	0	0	0	0	0	0	6
1999	4	2	0	1	0	0	0	0	0	7
2000	7	1	0	0	0	1	0	0	0	9
2001	6	0	1	0	0	0	0	0	0	7
2002	8	0	0	1	0	0	0	0	0	9
2003	9	1	0	0	0	1	0	0	0	11
2004	7	0	1	0	0	0	0	0	0	8
2005	3	3	0	0	1	0	0	0	0	7
2006	4	4	0	0	0	1	22*	0	0	31
2007	9	4	0	0	0	0	1	0	0	14
Total	255	27	3	4	4	4	23	0	1	322

*** The unusually high number of cases in 2006 due to the outbreak of rabies in dogs in the Limpopo Province**

the onset of the disease in dogs and in cats, is cause for concern.^{61,62,63} Success of transmission depends on a number of factors, particularly the number of bites, viral load, depth of bites, their location and presence or absence of clothing. Record review of untreated human cases suggests that the infection rates vary from virtually 100% with a short incubation period following severe, multiple bites to the head and neck, to 0,5% for bleeding, superficial bites through clothing.⁶⁴

A number of disturbing additional transmission routes have been described.^{46,65,66} Aerosol transmission has been documented in laboratory staff working with rabies virus and this route has also been suggested for individual cases where rabies was acquired in caves heavily infested with bats. For example in the laboratory-acquired cases high titered rabies virus infected materials were handled and incorrect handling of the material probably created virus-laden

aerosols. Because rabies is not a viraemic disease, it is not spread through occupational exposure to blood in health-care settings through surgical instrument or needle pricks, or blood transfusion.

Human-to-human transmissions have been reported in several transplantation cases in the USA and Germany, which included the transplantation of corneas, kidneys, liver, pancreas and arterial grafts.^{67,165-167} The possibility of transmission from an infected patient to family members has also been postulated in one Ethiopian study but is not substantiated.⁶⁸

Slaughtering and consumption of cattle and other animals that are subsequently confirmed as rabid have been reported. Although this practice is discouraged due to the risk of exposure to the rabies virus during the slaughtering process, ingestion of cooked meat from such animals have not been implicated in transmission of rabies virus to humans.⁶⁸ Due to the

The World Health Organization estimates the worldwide, annual number of rabies human deaths at about 55 000

risk of transmission during slaughtering, these cases are usually classified as category 2 exposures and require the administration of vaccine, or when physical injuries have been acquired during slaughtering as category 3 exposures.

As all mammals are susceptible to rabies, any infected mammal could potentially transmit rabies to humans. However mice, rats, shrews and monkeys have yet to be incriminated as vectors of rabies in South Africa. Rats and mice, particularly those kept as pets, frequently inflict retaliatory bites on children when cornered and caught. Rabies infection has never been confirmed in birds. Although bats have not been shown to transmit rabies virus (genotype 1) in South Africa, they are however vectors of rabies related viruses such as Duvenhage virus (genotype 4) and Lagos bat virus (genotype 2).

Preventing human rabies

Rabies is one of the top 10 global infectious causes of mortality and one of the most amenable to available preventive measures.⁶⁹ Primary care providers can play a crucial role in preventing rabies, by providing accurate prevention messages including the avoidance of suspicious animals, immunising people at high risk of rabies exposure, ensuring optimal wound management, and correctly administering immunoglobulin and rabies vaccine after suspected exposure to rabies virus.

Pre-exposure prophylaxis

A recent review found that at current rabies vaccine prices, routine use of pre-exposure vaccination is generally not cost-effective.⁷⁰ There are, however, particular high-risk situations where pre-exposure vaccination is cost-effective and it would be negligent not to recommend it. In South Africa the cost of pre-exposure prophylaxis is borne by vaccine recipients or their employers.

Pre-exposure vaccination involves administration of rabies vaccine on days 0, 7 and 28 (or day 21). Variation of a few days in the timing of second and third doses does not, however, affect the immune response. Currently, two vaccines are licenced for use in South Africa, the purified chick embryo cell culture vaccine and the purified vero-cell culture vaccine. These vaccines are considered safe and effective when administered according to the guidelines put forward by the World Health Organization.⁷¹

Practically all human rabies cases result from introduction of virus through broken skin by the bite of a rabies infected mammal

Rabies vaccine induces an active immune response that includes the production of neutralising antibodies. The antibody response requires approximately seven to 10 days to develop. The duration of persistence of this immune response is unclear as is the timing of booster vaccinations. Routine serological measurements of the vaccine recipient's blood can indicate the presence of levels considered adequate for protection. Virus neutralizing antibody levels of greater than 0.5 IU/ml are considered to be protective by the World Health Organization. A small study confirmed rapid boosting of antibodies up to 19 years after a previous vaccine course.¹⁷²

As it has repeatedly been found that people with intact immune systems experience a satisfactory response to approved vaccines, it is only necessary to demonstrate an adequate serological response in immunocompromised individuals or those working with live virus and those who are blood donors for rabies vaccines products.^{73,74} Rabies-neutralising antibodies are analysed by a neutralisation test. Two booster vaccinations (day 0 and day 3) should be administered to all vaccinated individuals that has had risk of exposure to rabid animals irrespective of their antibody titres and they should not receive immunoglobulin.⁴¹

Although a two-dose schedule (days 0 and 28) has also been investigated, results have confirmed the superior longterm immunogenicity of the three-dose approach for pre-exposure prophylaxis.⁷⁵

High-risk occupational groups

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. This should preferably be by administration of three doses of vaccine into the deltoid muscle on days 0, 7 and 28 (or day 21).⁷¹

Because the virus may be present in the saliva of patients with rabies, there is a potential risk of health worker exposure.⁷⁶

Human-to-human transmission has however never been reported under these circumstances. Infection control measures to protect health workers caring for patients with rabies should be instituted to protect against bites and exposure to infected saliva: gowns, gloves and goggles. Post-exposure prophylaxis with rabies vaccine may be considered in selected cases if there has been significant exposure i.e. a bite from an infected patient.¹⁶⁹ Surveillance staff responsible for bleeding dogs as a plague indicator species in rabies endemic areas are another occupational group that clearly merit pre-exposure vaccination.

Children in rabies-endemic areas

Routine vaccination could be beneficial for children in countries where rabies is enzootic. As children are particularly vulnerable and experience a higher frequency of bites to the head and neck as a result of their inclination to approach animals, there are advocates for inclusion of rabies vaccine in the Childhood Expanded Programme on Immunisation in rabies-endemic areas.⁷⁸ A controlled trial in Vietnamese children showed that combining purified rabies Vero cell vaccine with diphtheria, tetanus, whole-cell pertussis and inactivated poliomyelitis vaccine and administering these vaccines at two, three and four months, or alternatively at two and four months, resulted in all infants developing protective antibody concentrations against all five diseases with no serious adverse events.⁷⁹ A larger trial, also in Vietnamese infants, comparing intramuscular and intradermal vaccine administration demonstrated that both routes provided acceptable protective antibody titres (0,5 IU/ml).⁸⁰

Unfortunately current vaccine costs prohibit routine childhood vaccination against rabies. There is, however, a clear mandate for children to be formally educated on rabies transmission, the disease and prevention, particularly as educational interventions have proven effective in reducing the number of dog bites in children.^{81,82}

Rabies and travellers

Rabies is an important disease for the burgeoning travelling community. In the United States, for example, 37% of people dying from rabies are infected in foreign countries.²² Canine rabies is endemic in the some of the developing countries of Asia, Africa and South America. This poses a risk to travellers, particularly in the backpacking or adventure

category. Unfortunately discussion on reducing rabies risk is one of the topics often neglected by travel medicine advisors during pre-travel consultations.^{83,84} Travellers to these areas must be educated concerning their risk of rabies exposure and informed regarding local reservoir species so that they can avoid contact with potentially rabid animals. They should also receive instruction on correct wound cleaning, the importance of correct post-exposure prophylaxis with vaccine and immunoglobulin, and their availability at the traveller's destination.

Travellers with potential occupational exposure should certainly receive appropriate three-dose pre-exposure vaccination and this should also be considered for all long-term expatriate residents in high-risk areas, particularly those living in close proximity to the local population and their dogs.⁸⁵

Debate continues over the merit of administering routine pre-exposure vaccination for other categories of international travellers to rabies-endemic countries.^{71,86,87} The rate of animal bite exposure in international travellers has been estimated to be two to four people per thousand and in the majority of these cases there is some concern about rabies infection. However, where correct post-exposure prophylaxis is available, this is effective in preventing rabies and pre-exposure vaccination is of less importance. Although local reactions, such as pain, swelling and itching, occur in most vaccine recipients and mild systemic reactions, such as headache, nausea, muscle aches, abdominal pain and dizziness are reported by 5 to 40% of people vaccinated, serious adverse events are rare. The major constraint against routine administration remains the cost of pre-exposure vaccination. The cost, for example, of preventing rabies in United States tourists to Thailand by routine pre-exposure vaccination was estimated at between US\$ 40 to 50 million per rabies death prevented.⁸⁸

The death of a human from rabies should be viewed as a health system failure

On the other hand, areas where stray dogs are a problem are often the specific areas where canine rabies is endemic, and efficacious vaccines and immunoglobulin are not available.

Fraudulent vaccines, nerve-tissue derived vaccines and equine immunoglobulin commonly associated with severe adverse reactions may be used in these countries.⁸⁹ In certain areas tourists are frequently exposed to dogs, for example a survey of European travellers in Thailand found that in less than a three week period 1,3% of tourists experienced dog bites and 8,9% dog licks.⁹⁰ Advantages of pre-exposure rabies vaccination include requiring only two boosters, on days 0 and 3, if there is an exposure, no need for immunoglobulin, and diminished concern about inadequate therapy and vaccine failure.

Advice and vaccination should be adapted to the individual needs and exposure risks of travellers, taking into account the area visited, local rabies epidemiology, mode of travel, and underlying medical conditions and medication. Travellers who are immunocompromised by disease or selected medications are a group deserving particular attention as immune response to vaccine may be suboptimal. They should avoid activities for which rabies pre-exposure vaccination is indicated. When this is not possible, immunocompromised individuals who are at risk of rabies exposure should be vaccinated and their antibody titres checked post-vaccination.⁹¹

Management of humans exposed to rabies

The death of a person from rabies should be viewed as a health system failure. This contention is supported by a review of failed post-exposure prophylaxis in Thailand, which found that delays, failure to provide post-exposure prophylaxis or deviations from the recommended regimen contributed directly to the deaths of young children.⁹²

Findings from studies in South Africa and Thailand have highlighted deficiencies in health workers' knowledge on managing suspected rabies exposures.^{49,93}

It is therefore recommended that a confidential enquiry routinely be conducted to establish avoidable factors which may have contributed to the death.

Although no controlled human trial of rabies post-exposure prophylaxis utilising wound treatment, immunoglobulin and vaccination has been conducted and such a study would be unethical, extensive global experience provides convincing support for this approach.^{94,95,96}

There is a critical need for veterinary and health workers to be adequately trained on assessing rabies risk and appropriate response. It is also imperative that health and veterinary workers involved in managing human cases with potential exposure to rabies virus remain in close communication so that patient management can be modified by data about the source animal. The health worker is obliged to make contact with the responsible state veterinarian. Laboratory-confirmed human rabies and exposure to proven rabid animals is notifiable in South Africa.

Assessing risk after exposure

Important factors that assist decisions on prophylaxis, include details of the nature of the contact and the implicated animal's behaviour.⁹⁷ It is imperative that prophylaxis be instituted as soon as possible after exposure to rabies virus, even before there is laboratory confirmation of rabies in the animal.⁹⁸ Ideally post-exposure prophylaxis should be administered to all bite victims, but availability and costs of the biologicals is a problem. The approach adopted in South Africa focuses on providing prophylaxis to those individuals at high risk of rabies infection.

To reduce the risk of rabies, it is important that thorough cleaning of the bite wound is initiated as soon as possible

Judgement on whether to initiate post-exposure prophylaxis is assisted by an estimation of risk based on the following criteria, with a high risk of exposure necessitating vaccination:⁴¹

- type of contact. Bats may be involved in transmitting rabies-related viruses, i.e. Duvenhage and Lagos Bat viruses, and any encounters should be considered. Small rodents eg. mice and rats commonly found in and around dwellings are not typically associated with rabies. To date in South Africa there has only been one transmission of rabies associated with a bite from a baboon. (Fig. 7, pg 41 or Appendix 2)
- incidence of rabies in the animal's district of origin
- animal's behaviour (any abnormal behaviour could indicate rabies)
- species of animal involved (Table 2, page 10)
- vaccination status of animal (if not vaccinated, then higher risk)*

- results of rabies laboratory testing (a negative result from an approved rabies veterinary laboratory indicates a lower risk)
- when the biting animal cannot be traced, caught or identified, or the brain is not available for laboratory examination, it should be assumed that the animal was rabid.
- * An animal vaccinated before 3 months of age with no boosters may not be protected from rabies.

There is no blood test for the human victim that can confirm or exclude transmission of rabies virus from an infected animal.

Any decision to provide post-exposure prophylaxis is made on the risks of the exposure to the human victim. Post-exposure prophylaxis should not be delayed pending the results of rabies laboratory tests in the animal

The most important criteria are the non-availability for assessment of the biting animal in an endemic area, abnormal behaviour in the animal and type of contact. A diagrammatic representation of the recommended approach is given in Fig. 7 (page 41 or Appendix 2). If in doubt, it is preferable to vaccinate.”

In the case of AIDS patients (or otherwise immunosuppressed patients) it is particularly important to focus on thorough wound care when a rabies virus exposure is suspected. The immune response to rabies vaccine has been shown to be decreased in HIV infected persons. It is therefore advised that human rabies immunoglobulin be administered together with vaccine not only for category 3, but also for all category 2 exposures for these patients. No other deviations to the number of doses or schedules for administration are currently advised.

Management of the wound

To reduce the risk of rabies, it is important that thorough cleaning of the bite wound is initiated as soon as possible. The bite wound should be copiously flushed immediately for 5 to 10 minutes with water or soap and water, while irrigation of deep puncture wounds, for example following a feline bite, should be performed using a syringe. If antiseptic is available, for example a 1 in 20 dilution of 5% chlorhexidine in water, then this may be added to the water. Bleeding should be encouraged and wound suturing

should preferably be avoided or delayed.⁹⁹ Applying an iodine-based disinfectant or 70% alcohol to the wound after flushing is also indicated, as these chemicals inactivate rabies virus.⁶⁹

To lessen the risk of bacterial infection, antibiotic therapy should be considered. As most infections following mammalian bites comprise multiple pathogens, with mixed aerobic and anaerobic species, it is essential that therapy should be selected appropriately.^{100,101,102} In addition to the usual aerobic and anaerobic bacteria, important potential pathogens include *Pasteurella multocida*, which is isolated in 20 to 30% of dog-bite wounds, and is particularly associated with cat bites, and can cause serious infection with severe complications, and *Capnocytophaga canimorsus*, which can induce sepsis following apparently minor bites particularly in immunocompromised individuals particularly those without a functioning spleen.^{103,104}

Antibiotic therapy is modified in line with laboratory culture and susceptibility results when a patient requires hospitalisation as a result of severe local or systemic sepsis. Additional indications for hospitalisation include penetrating injuries of tendons, joints or the central nervous system, severe bites to hands or head and neck, patients requiring reconstructive plastic surgery and patients with certain high-risk medical conditions, for example diabetes, asplenia and peripheral vascular disease.

The administration of antirabies immunoglobulin complements rabies vaccination in situations where viral transmission may have occurred

To prevent tetanus, a booster dose of tetanus toxoid (TT) adsorbed vaccine (0,5 ml intramuscular) should be given at the time of wound treatment in individuals who have completed a primary course of tetanus vaccination. Most adult tetanus cases occur in people who do not have a vaccination history.¹⁰⁹ However, the benefits of regular tetanus boosting throughout adult life are insufficient to justify the costs of an administration programme and potential sensitivity reactions.¹¹⁰

Human antirabies immunoglobulin

The administration of antirabies immunoglobulin (RIG) complements rabies vaccination in situations where viral transmission may have occurred, as production of vaccine-induced neutralising antibodies take seven to 10 days after vaccination. RIG is safe and provides rapid passive immunity that persists with a half-life of approximately three weeks.^{111,112}

The human RIG currently used in South Africa is produced by fractionation of pooled serum from immunised persons. The introduction of human RIG proved a valuable replacement to the previously used antirabies serum prepared in horses. Although the latter was effective and is still used in many developing countries, it may induce serum sickness. To ensure potency, it is essential that RIG be maintained between 2 and 8°C during handling and storage. All patients who have received RIG should be observed for an hour thereafter. An emergency pack for treating anaphylaxis should be available.

The dosage of human RIG currently available in South Africa is 20 International Units (IU) per kg body-mass.⁷³ RIG is supplied in 2 ml ampoules with a virus-neutralising antibody content of 300IU. Preferably the complete dose of RIG should be infiltrated into the depth of the wound or tissue immediately adjacent to the wound. Where this is not anatomically possible, the remaining RIG may be injected intramuscularly into the deltoid muscle.¹¹³ RIG was traditionally administered into the buttocks, but there is evidence of low circulating rabies neutralising antibodies following RIG injection into gluteal fat. With multiple wounds, where the dose of RIG based on body mass is insufficient to infiltrate all wounds, the dose must be diluted up to 50% in saline to allow infiltration of all wounds. Failure to infiltrate all wounds is believed to have contributed to the deaths of a number of children.¹¹⁴ Local anaesthetic agents should not be used to facilitate RIG administration.

RIG is administered on the day of initial patient presentation, traditionally referred to as day 0, with the first dose of vaccine but at separate injection sites. This is irrespective of the time elapsed since exposure, which represents a departure from the previous recommendation that RIG should only be given to patients presenting within a week of exposure.⁹⁷ If RIG is not available when vaccination is initiated, it may be administered up to day 7 after the administration of the first vaccine. RIG administration is not recommended prior to vaccination, nor is it currently recommended for individuals who have received pre-exposure vaccination as it is believed that RIG may interfere with the rapid anamnestic response to vaccine.

Rabies vaccines

Rabies vaccine, when given post-exposure, induces immunity within seven to 10 days. Two cell-culture vaccines are currently registered for use in South Africa, i.e. purified chick embryo cell culture vaccine (PCECV) and purified Vero-cell rabies vaccine (PRVR), and are highly purified and inactivated vaccines that meet the WHO potency standard of greater than or equal to 2,5 IU per dose.

All persons judged to be at high risk for rabies exposure should be vaccinated, with treatment being initiated as soon as possible even if there has been a delay in presentation to the health service. The treatment/prophylaxis schedules presented here are based on the most recent WHO recommendations, and are valid for the cell-culture vaccines registered in South Africa. However, it must be emphasized that the Essen intramuscular regimen is the only recommended schedule and administration route for South Africa, and expert advice should be sought before using an alternative regimen. The vaccination schedule may be discontinued if the suspected source animal remains healthy for 10 days after the exposure or if an approved veterinary laboratory reports the brain specimen from the animal as negative.⁴¹

TABLE 10: WHO-approved post-exposure rabies vaccination regimens¹⁵⁹

Regimen	Summary	Day (number of sites)						
		0	3	7	14	21	28	90
Essen (IM 1 x 5)	One dose into deltoid on each of five visits	✓ (1)	✓ (1)	✓ (1)	✓ (1)		✓ (1)	
Zagreb (IM 2-1-1)	Double dose IM (1 dose at 2 sites) on day 0, followed by single doses on days 7 and 21	✓ (2)		✓ (1)		✓ (1)		
Thai Red Cross (ID 2-2-2-0-2)	Double 0,1ml dose ID (1 dose at 2 sites) on days 0, 3, 7 and 28	✓ (2)	✓ (2)	✓ (2)			✓ (2)	
Oxford (ID 8-0-4-0-1-1)	Eight 0,1ml doses in separate sites on day 0, then four 0,1ml doses on day 7 (separate sites), then single doses at 28 and 90 days	✓ (8)		✓ (4)			✓ (1)	✓ (1)

The *standard*, or *Essen schedule* (Table 10) of vaccination may be used in all types of exposure to infection requiring immunisation. A single dose of vaccine is administered intramuscularly into the deltoid of adults or into the anterolateral thigh of infants or children less than one year of age on days 0, 3, 7, 14 and 28 of treatment. Vaccine should not be injected into the buttock as fat depots may interfere with vaccine uptake and to avoid injury to sciatic nerves. On day 14, persons who have received any of the recommended cell culture vaccines on days 0, 3 and 7 should have protective levels of virus-neutralising antibodies.^{115,116,117} Persons who have received pre-exposure vaccination should be given only two booster doses of vaccine on days 0 and 3 (with no RIG) if they experience a category 2 or 3 exposure by a suspect rabid animal.

A second intramuscular regimen approved by WHO but not adopted in South Africa is the 2-1-1 *Zagreb* intramuscular regimen (Table 10). This abbreviated schedule is usually advocated for use only in risk category 2 (not category 3) exposure victims. This approach aims to induce a rapid endogenous immune response. The use of RIG simultaneously with this schedule is controversial although there is no evidence that immunoglobulin given

in this way suppresses the immunogenicity of rabies vaccine.^{97,120} Two doses of vaccine are given intramuscularly on day 0, into both deltoids in adults or anterolateral thighs in infants and children less than one year, and this is followed by single intramuscular doses on days 7 and 21.

More recently multisite intradermal (ID) regimens with cell-culture vaccines have demonstrated great effectiveness in specific situations while being more affordable.^{97,121} Both the Thai Red Cross and Warrell's Oxford multiple site intradermal schedules are highly immunogenic without notable suppression from RIG administration on day 0 (Table 10).¹¹⁴ The *Thai Red Cross* two-site intradermal method consists of one ID dose at two sites on day 0, 3, 7 and 28. The 8-site intradermal method consists of 1 ml HDCV or purified chick embryo vaccine divided between 8 intradermal sites on day 0, i.e. deltoids, anterior thighs, suprascapular and lower quadrant of abdomen bilaterally, and then 0,1 ml intradermally administered at four sites on day 7, i.e. bilaterally into deltoids and thighs, and then single 0,1 ml intradermal doses on day 30 and day 90. Although the intradermal schedule has proven effective it should not be used in immunocompromised individuals is not currently recommended in South Africa.¹²² It is recommended that the same

Preferably the complete dose of RIG should be infiltrated into the depth of the wound or tissue immediately adjacent to the wound

vaccine product be used for an entire vaccine series. It may however be necessary to change the product when the patient exhibits sensitivity to the one product.¹⁷⁰

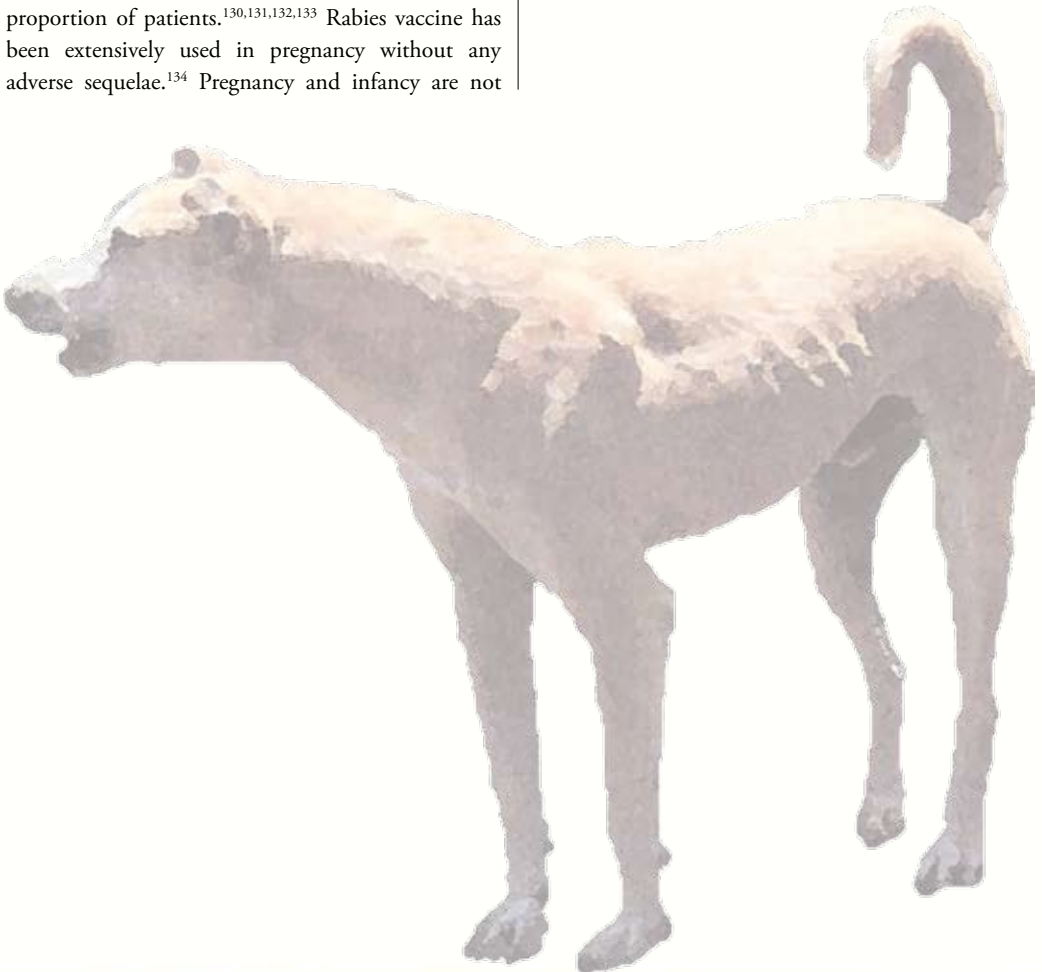
Unlike earlier central nervous system derived vaccines, for example Semple and suckling mouse-brain products, PCECV and PVCV, have an excellent safety profile. The former vaccines are still widely used in developing countries because of their affordability. However, their uncertain immunogenicity and accompanying risk of severe neurological adverse reactions, with a frequency of between 1 in 120 to 1 in 1 200 vaccine recipients, make them a poor option.^{124,125,126}

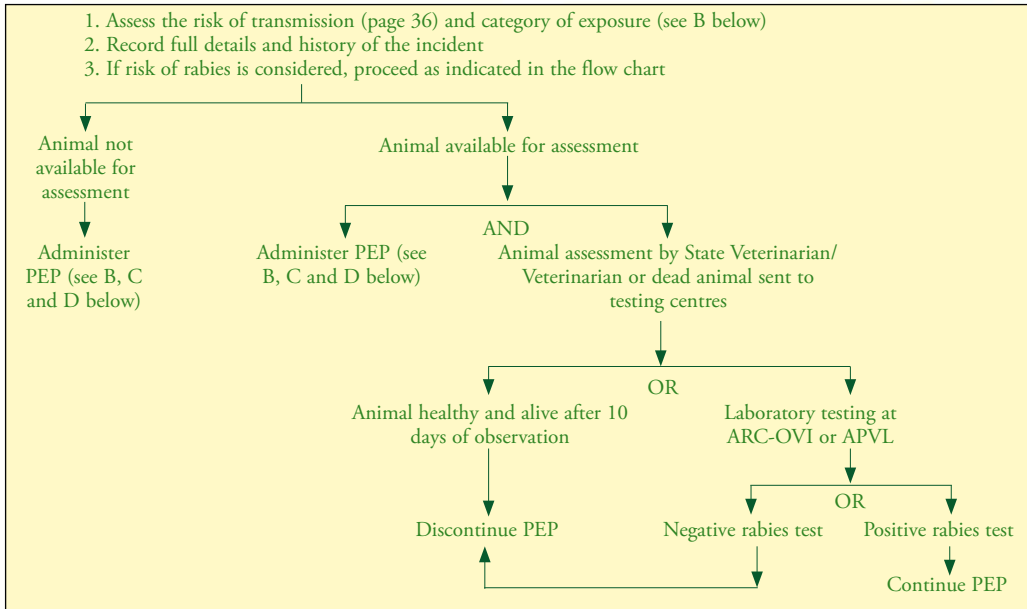
Adverse events to modern cell culture vaccines are uncommon and severe reactions are exceedingly rare with these vaccines.^{127,128,129} Single cases of peripheral polyneuropathy, and other local and systemic reactions such as itchiness, fever, urticaria and arthralgia are experienced in a very small proportion of patients.^{130,131,132,133} Rabies vaccine has been extensively used in pregnancy without any adverse sequelae.¹³⁴ Pregnancy and infancy are not

contraindications for rabies vaccination with cell culture vaccine if the risk of rabies virus transmission is considered significant. Any adverse events should be notified to the relevant provincial and national officials for full investigation.

It is essential that the cold chain be maintained with rabies vaccine kept between 2 and 8 °C during all handling and storage. Vaccine must be used on the day opened. Unused vaccine must be discarded. All patients should be observed for an hour after receiving vaccine and an emergency pack for treating anaphylaxis should be available.

The flow diagram in Fig. 7 (page 41 or Appendix 2) provides a useful approach to the person with a suspected rabies exposure. This should be reproduced and made available in all clinics and hospital casualty units in rabies endemic areas.





A. Animal Assessment

The following aspects must be considered:

1. Vaccination: tangible proof of current rabies vaccination status (dog or cat) must be obtained. See constraints on page 36
2. Behavioural changes: all aspects must be considered
3. Possible exposure: any known incident during the previous few months
4. Rabies endemicity: entire RSA is rabies endemic but current incidence and prevalence are important
5. Provocation: was the animal's reaction due to provocation?
6. Stray (unsupervised animals): this history may be unreliable

B. Categories of rabies exposure

Risk Cat.	Type of exposure	Action to be taken
1	Touching/ feeding animal Licking of intact skin	None if case history is reliable If history is not reliable, treat as for category 2
2	Nibbling of uncovered skin Superficial scratch without bleeding	Apply wound treatment Administer vaccine Do not administer antirabies immunoglobulin Stop vaccination if animal is rabies negative on laboratory test, or remains healthy after 10 days observation
3	Bites/scratches which penetrate the skin and draw blood Licking of mucous membranes or broken skin	Apply wound treatment Administer vaccine Administer antirabies immunoglobulin Stop vaccination if animal is rabies negative on laboratory test, or remains healthy after 10 days observation

C. Wound treatment

1. Flush well with soap and water or water alone for at least 5 minutes and apply disinfectant eg. 70% alcohol or iodine solution (eg. Betadine)
2. Avoid suturing or use of compressive bandages
3. Administer anti-tetanus treatment and antibiotics if indicated

D. PEP schedules

No previous immunization

Category 2: Inject single dose vaccine into deltoid muscle (NEVER in gluteus) or antero-lateral thigh in children on days 0, 3, 7, 14 and 28

Category 3: Infiltrate immunoglobulin (20 IU/kg) on day 0 into and around wound, with remainder into deltoid of opposite arm to vaccine. Inject vaccine as for category 2. Rabies immunoglobulin if not immediately available can be given up to 7 days of the first vaccine dose, but never after 7 days

Previously immunized

Category 2 and 3 exposures: Inject single dose vaccine into deltoid muscle on days 0 and 3. No rabies immunoglobulin should be given

Special considerations

Late presentation: Treat without delay as if the contact occurred recently, following the guidelines for wound treatment (where possible), and administration of immunoglobulin and vaccine. Deviation from the suggested doses/regimens is not advised.

Immunosuppressed patient: Emphasize thorough wound cleaning and ALWAYS administer antirabies immunoglobulin in both category 2 and 3 exposures in addition to the vaccine. Deviation from the number of doses and prescribed regimens is not advised.

Bat exposures: PEP provides variable protection against rabies-related viruses. The categories of exposure do not apply to bats, as transmission can occur with very minor or even inapparent contact. Any close contact with bats is considered as a category 3 exposure.

Fig. 7: Actions following a human exposure to a suspected rabid animal

Diagnosing human rabies

The clinical features of rabies, particularly in the terminal stages of the disease, reflect the neural nature of the pathology. Conditions that cause an acute or subacute encephalopathic picture may be confused with rabies, therefore a definitive diagnosis is important to identify conditions amenable to therapy.

Clinical picture

The highly variable incubation period of human rabies is a phenomenon that is not understood completely.^{69,135}

Deep or multiple bites, particularly to the head and neck, may result in an incubation period of less than two weeks. However, incubation periods exceeding two years are also well documented.¹³⁶ Generally incubation periods seldom exceed 90 days and usually range between two and eight weeks, with 90% being less than six months.

Nonspecific prodromal features last for one to four days and include fever, headache, malaise and nonspecific gastrointestinal symptoms. Neuropsychiatric symptoms, including irritability, depression, anxiety and insomnia, may be present. Sensory symptoms at the bite site, which has usually healed, are commonly experienced and may include intense pruritis, paraesthesia or pain.

Following the nonspecific prodromal symptoms is a period lasting one to six days during which neurological signs and behavioural symptoms dominate. These include agitation and restlessness, incoherent or illogical speech and psychomotor hyperactivity, including episodic terror, hallucinations and manic behaviour, or generalised convulsions that may be triggered by various sensory stimuli. A remarkable and tragic feature distinguishing rabies from other acute encephalopathic neurological conditions are the lucid periods during which patients are well orientated.

As the disease continues there is progressive loss of neurological function. This is characterised by an inability to swallow (dysphagia), speech involvement

(dysarthria), hypersalivation and spasms of the involuntary musculature with resultant classical hydrophobia, or fear of water.¹³⁶ Aerophobia, following exposure to air movement, is another typical symptom. Focal neurological abnormalities are surprisingly rare, while tachycardia and hyperpyrexia are more frequent. Convulsions and muscular spasms become prominent as the patient's mental state deteriorates with progressive disorientation, hallucinations, confusion and coma.

Other clinical presentations include priapism, excessive libido and spontaneous pneumomediastinum.^{137,138,139} Patients usually die within five days of disease onset as a result of progressive cardio-respiratory failure, often preceded by obvious central nervous system respiratory irregularity. Progression to a nonreactive electroencephalograph (EEG) or sudden demise during a generalised seizure are common terminal events.

Occasionally the agitated phase is absent and progressive paralysis as a result of spinal cord affection is the prominent feature.¹⁴⁰ This may be asymmetrical, particularly affecting the limb that was bitten, or may mimic acute flaccid paralysis with symmetrical ascending paralysis and sphincter involvement but with accompanying sensory disturbance. Death from respiratory and bulbar paralysis in this form of rabies usually follows a longer period of clinical illness than seen with furious rabies.

Common complications include respiratory arrest, pneumonitis, hypoxia because of ventilation-perfusion abnormalities, cardiac arrhythmia, interstitial myocarditis, posterior pituitary disorders, internal hydrocephalus and gastrointestinal bleeding.

Although there have been reports of human survival despite clinical disease, less than half a dozen are accepted as authentic, and intensive supportive hospital care appears to have been an essential element in each of these cases.^{141,142,143} In South Africa and similar developing countries where medical attention is usually sought late and sophisticated intensive care facilities are not available, most patients succumb within one to three days of hospital admission.¹³⁶

TABLE 11: Differential diagnosis of rabies in humans (adapted from Warrell¹⁴⁰)

• Hysterical pseudo-hydrophobia
• Tetanus
• Encephalitides, including other viral infections
• Delirium tremens
• Various chemical intoxications
• Postvaccinal encephalomyelitis
• Behavioural disorders, including acute psychiatric presentations
• Typhoid fever
• Poliomyelitis
• Acute flaccid paralysis

Confirming rabies in humans

The clinical picture is almost definitive in rabies endemic areas. A history of contact with an animal proven to be rabid makes the diagnosis more reliable. There are two reasons for establishing a definite diagnosis of rabies prior to demise. Firstly, the prognosis is so devastatingly poor that relatives may demand, and deserve, a definite diagnosis. Secondly, it would be negligent to withhold therapy for another treatable condition if rabies was not the cause of the illness.

No laboratory test currently exists to diagnose rabies during the incubation period. Even after the onset of clinical signs, laboratory diagnosis is not simple and negative results do not preclude rabies. It is therefore often necessary to perform complementary tests on different specimens or even to repeat tests (see appendix I).¹⁴⁴

Reverse transcription polymerase chain reaction (RT-PCR) detects the viral genome and is the preferred test for ante mortem diagnosis of rabies in most laboratories. Saliva, CSF or nuchal biopsy specimens may be used for RT-PCR. It is important that saliva specimens be collected for testing, and not sputum (respiratory track exudates). Virus may also be isolated from saliva or CSF specimens. Spread of virus from the brain in nerve fibres to the eye and nerve networks around hair

follicles, may allow detection of antigen by fluorescent antibody testing in corneal impression smears or nuchal skin biopsies, but are not performed routinely in all laboratories.²⁶

Serum antibody can only be detected late during clinical disease (after five days), or seven to 10 days after vaccine administration. Detection of serum antibody is only diagnostic in unvaccinated patients. CSF serology may also be problematic, since antibody is usually only detectable late during clinical disease (after five days). Detection of antibody in the CSF is however diagnostic, since vaccine-induced antibody only penetrate the blood-brain barrier under exceptional circumstances.

An antemortem brain biopsy may rarely be justified to eliminate rabies as a differential diagnosis, for example where herpes encephalitis is suspected.⁶⁴ Histopathological examination of brain sections for the presence of viral intracytoplasmic inclusions in neurons, the Negri bodies, is a painstaking procedure and often unreliable.

If diagnosis is not confirmed prior to death, then postmortem diagnosis should be made. Medical practitioners who will be responsible for performing autopsies should receive standard pre-exposure vaccination against rabies and take careful infection control precautions when obtaining specimens. These include wearing an impervious gown and apron, gloves and a visor.¹⁴⁵ The ideal postmortem brain specimen is the entire brain, with the two halves preserved separately in 50% glycerol saline and 10% buffered neutral formalin in sealed, plastic screwtop jars for virological and histological examination, respectively but matched small cubes (1–2 cm) of cerebrum, cerebellum, hippocampus, medulla, thalamus and brainstem stored in a similar way may also be submitted. Necropsy diagnosis can also be

done by taking a brain biopsy specimen with a trucut needle inserted through the superior orbital fissure into the cranial cavity.¹⁴⁶ This latter technique has the advantage of avoiding a full necropsy where the deceased's relatives are opposed to it and reduces the number of health personnel exposed. Careful labelling and

A remarkable and tragic feature distinguishing rabies from other acute encephalopathic neurological conditions is lucid periods during which the patients are well orientated

packaging in secure rigid secondary, and where possible tertiary, containers filled with absorbent material (paper or sawdust) and direct communication with the National Institute for Communicable Diseases is essential before the specimen is dispatched by courier. All rabies diagnostics for suspected human cases are carried out by the Special Pathogens Unit of the National Institute for Communicable Diseases of the National Health Laboratory Service.

Managing clinical rabies

The almost universally futile nature of clinical rabies management makes it imperative that relatives of the victim be honestly counselled as to the extremely poor prognosis. Every effort must be made to ensure a patient's comfort with adequate sedation, while high-quality supportive care is provided. It should be emphasised that although lifesupport measures may prolong the clinical course of disease, they are unlikely to result in survival, except in extremely rare occasions.^{22,147, 183} The so-called Milwaukee protocol which was followed in the treatment of a rabies survivor patient is regarded as experimental.

Concerted efforts must be made to ensure that the patient is as comfortable as possible and symptoms alleviated. This includes adequate sedation and pain relief with opioids and anxiolytic treatment, maintenance of nutrition and correction of fluid-electrolyte and acid-base balances, and mechanical respiration.⁹⁹ As multiple systems bear the brunt of terminal disease, careful monitoring is necessary. Antiviral drugs, particularly interferon and interferoninducers, have been employed with little success.¹⁴⁸ Corticosteroid use has not proven effective and antirabies vaccine has no proven benefit in treatment. Intensive nursing care may limit complications, such as bedsores and pneumonia.

Infection control precautions are important for health workers responsible for managing these patients and should include both standard precautions (hand washing, gloves, mask, eye protection or a face shield, gown and plastic apron) and respiratory precautions (isolation in a private room preferably with an extraction fan, wearing respiratory protection and limiting the movement of the patient).^{145,149} If a staff member is exposed to potentially contaminated secretions, e.g. patient saliva contamination of a mucous membrane, then they should immediately receive post-exposure prophylaxis, by flushing with copious clean water and vaccination according to

their vaccination status.

The rabies virus is not particularly resistant and is inactivated by heat, sunlight and desiccation. Objects soiled by infective secretions must be disinfected by boiling or autoclaving.⁷⁴

Disposable items used in treating patients should be incinerated. Surgical instruments should be autoclaved, while other items in the patient's environment should be cleaned with an appropriate disinfectant, containing chlorine (10 000 ppm available chlorine) or glutaraldehyde. The corpse of a rabies victim is thought to pose little risk but it is prudent to avoid embalming the body.⁷⁴

In a well documented case report of survival, that of a six-year old boy bitten by a rabid bat in the United States of America, it appears that careful monitoring and rapid supportive therapy to prevent hypoxia, intracranial hypertension, cardiac arrhythmias, seizures and nosocomial infection, may have contributed to his recovery.¹⁴² The only human case of surviving rabies without any history of receiving rabies prophylaxis was reported in a teenage girl from the United States who was exposed to a rabid bat. The patient developed rabies and a decision was made to institute experimental treatment which included an induced coma and administration of several drugs.¹⁸³ The patient recovered with some neurological sequelae but continual improvement of her condition has been noted.

Serum antibody can only be detected after onset of clinical disease, or seven to 10 days after vaccine administration



Plate 31: This child appeared to be thirsty but pushed the glass away when water was offered. Such behaviour is referred to as hydrophobia



Plate 32: A child with rabies showing marked anxiety



Plate 33: Death is inevitable when rabies clinical signs become apparent and consoling the family members must be given priority



Plate 34: Generalised seizures are seen in preterminal rabies. Seizures may be elicited by sensory stimuli such as air movement, sound and attempts to drink

RABIES LEGISLATION

Human rabies and the law

There are a number of important legal considerations relating to the diagnosis, management and reporting of rabies in humans in South Africa.

Negligence

When deciding whether a doctor has been negligent the court assesses whether the doctor concerned acted as a “reasonable medical practitioner would have done under the same circumstances”.¹⁵⁰ Four questions are usually considered; if the first two are satisfied then the accused person is said to have owed the injured person a “duty of care”. Whether this has been breached is determined by answering the next questions.

The questions are:

- Would a reasonable medical practitioner in the same position have foreseen harm?
- Would a reasonable medical practitioner have taken steps to guard against occurrence of harm?
- What steps would a reasonable medical practitioner have taken to prevent the harm?
- Did the accused take these steps?

The more serious the potential results and the greater the likelihood that harm will occur, the greater the possibility that the courts will impose a duty of care.

Therefore, with the existence of national guidelines on the management of persons potentially exposed to rabies in South Africa, breach of these guidelines, for example failure to adequately treat the wound, failure to notify a state veterinarian or police officer about the existence of a potentially rabid animal, failure to complete the correct regimen of post-exposure prophylaxis, would most likely be considered unreasonable care and therefore negligence.¹⁵¹

The Health Act (Act No. 63 of 1977)

In terms of section 45 of the Health Act (Act No. 63 of 1977) rabies is a notifiable disease. It is therefore required that the responsible local or provincial authority and state veterinarian be informed of any human rabies case, death or contact on the prescribed form, GW17/5. Rabies is unique as it is the ONLY notifiable disease where contact by a person with an infected animal is also notifiable.

Postmortem

A suspected rabies death should be considered as due to an unnatural cause. A definitive diagnosis is of particular importance where an animal owner may be liable for not ensuring that his/her dog or cat was vaccinated according to legal requirements. A postmortem should be requested and although relatives should be counselled, consent to conduct the postmortem is not necessary.

Animal rabies and the law

The Animal Diseases Act (Act No. 35 of 1984) provides for the control of specific animal diseases and for measures to promote animal health.³⁸ The Minister of Agriculture may make regulations for accomplishing the purposes of the Act and has determined that rabies control measures should be applied throughout the country. The decision was based on the geographical distribution of animal rabies cases diagnosed over a five year period from 1995 to 1999.

The Animal Disease Regulations identify rabies as a controlled animal disease. Table 12 describes the general rabies control measures applicable in South Africa.

TABLE 12: Rabies control regulations

Animal disease	Nature, causal organism and symptoms	Susceptible animals	Controlled veterinary Act to be performed in respect of:		
			Susceptible animals	Contact animals*	Infected animals
1	2	3	4	5	6
Rabies	Fatal, viral disease to which man is also susceptible, mainly transmitted by the bite of an infected animal and characterised by behavioural deviation, salivation, aggressiveness, progressive paralysis and abnormal vocalisation		<p>All dogs and cats in the Republic shall be immunised with an efficient remedy by an officer, veterinarian or authorised person at the age of three months followed by a second vaccination within 12 months, at least 30 days after the first vaccination and thereafter every three years</p> <p>Dogs and cats younger than three months may be vaccinated provided that they are again vaccinated at the age of three months, followed by a third vaccination within 12 months and thereafter every three years</p>	Contact animals shall be isolated and immunised with an efficient remedy by or under the supervision of a veterinarian, an officer or authorised person, unless the state veterinarian decides to destroy the animals	Infected animals shall be isolated and destroyed by the responsible person or an officer, veterinarian or authorised person: provided that a responsible person who destroys such animal shall retain the carcass for the attention of an officer, authorised person or veterinarian

* *Contact animals are animals that have been, or are suspected to have been, bitten or scratched by a rabid animal, or received saliva, brain or other infectious material from a rabid animal into a wound, the mouth or eyes*

All suspected outbreaks of rabies must be reported to the responsible state veterinarian or animal health technician for investigation. This may include euthanasia of the suspected animal after which brain samples are submitted to confirm the diagnosis. If symptoms are not suspicious, the animal may be kept in quarantine under observation for a period determined by the state veterinarian.

Vaccination

Vaccination is a cost-effective method of protecting companion animals against rabies. Safe and efficacious vaccines that induce a protective immunological

All dogs and cats regardless of their age, weight or pregnancy status may safely be vaccinated

response within two weeks of vaccination are readily available. Vaccination adverse events are extremely rare and if they occur, generally mild. All dogs and cats in South Africa must be vaccinated strictly according to the regulations, which read as follows:

“All dogs and cats in the Republic shall be immunised with an efficient remedy by an officer, veterinarian or authorised person at the age of three months followed by a second vaccination within 12 months, at least 30 days after the first vaccination and thereafter every three years. Dogs and cats younger than three months may be vaccinated provided that they are again vaccinated at the age of three months, followed by a third vaccination within 12 months and thereafter every three years.”

The administration of vaccine before three months of age is justified by the incidence of rabies in puppies in South Africa. The Southern and Eastern African Rabies Group agreed at their conference in Nairobi in 1997, that there was no age below which vaccination of a dog against rabies would not be effective. There are definite benefits in vaccinating very young puppies, especially in areas of high prevalence where the chances that the dog will not present again for vaccination are high. As vaccine coverage is low in many dog populations, it can be assumed that few puppies will have significant passive protective neutralising antibodies to reduce the efficacy of vaccination.

During a mass vaccination campaign in Tunisia puppies less than three months of age responded to vaccination with no significant interference by passive maternal immunity.¹⁵² Dogs of all ages, even those less than three months of age, should be included in rabies mass vaccination campaigns.

All dogs and cats regardless of their age, weight or pregnancy may safely be vaccinated. Rabies vaccines may be safely administered on their own or together with canine distemper, adenovirus type 2, parainfluenza, leptospirosis and parvovirus vaccines.

It is usually not economically feasible to vaccinate all livestock against rabies. However, consideration should be given to vaccinating livestock that are particularly valuable, kept in areas of high-risk or during focal epidemics caused by black-backed jackal. Wild mammals kept as pets should probably be vaccinated annually, although trials have not been performed in these species to determine vaccine efficacy or the ideal vaccination schedule.

All parenteral rabies vaccines registered in South Africa must be inactivated and induce at least three years protection following primary vaccination.

Interprovincial movement restrictions

As South Africa in its entirety is considered a rabies endemic area, all interprovincial movements of dogs and cats must be accompanied by a valid rabies vaccination certificate.

Puppies and kittens less than three months of age may be vaccinated at weaning and can then be moved immediately to any destination in the country provided that they are revaccinated at three months of age. The rabies vaccination certificate of an appropriately vaccinated dog or cat is valid for three years in South Africa.

All carnivorous wild animal species, including jackal, mongoose, bat-eared fox, wild dog, lion, leopard, cheetah and hyena must be vaccinated against rabies with an inactivated vaccine before being moved anywhere in South Africa and all movements must be accompanied by a valid rabies vaccination certificate.

Export from South Africa

The Department of Agriculture's veterinary health certificate must be completed for international movements (Fig. 8). All vaccinations performed for international movements may only be carried out by an authorised person using a registered vaccine. When this certificate is completed by a registered private practitioner, it must be endorsed by a state veterinarian.

Conditions for importation and validity of rabies vaccinations are determined by the importing country. The onus is on the owner to determine the requirements of an importing country. South Africa presently has agreements with Botswana, Lesotho, Malawi, Namibia, Swaziland and Zimbabwe, and these countries accept dogs and cats from South Africa accompanied by a valid vaccination certificate, where the certificate is signed by a state veterinarian, registered private veterinarian or authorised government veterinary official.

Immunity is only considered valid 30 days after the date of vaccination and remains valid for 12 months. Puppies and kittens under three months of age can be exported provided that their mother was vaccinated against rabies at least one month but not more than 12 months prior to the birth of the litter. This information must be recorded on the veterinary health certificate as required by the importing country.

Where booster inoculations are administered before the expiry date of previous vaccinations, the certificate is valid with immediate effect.

Import into South Africa

The present import permit required for importation or reimportation of dogs or cats into South Africa requires a health declaration certifying:

- the residential status of the animal in the exporting country
- that the area of origin is not under veterinary restriction for any disease to which carnivores are susceptible
- that they have not been in contact with animals infected or suspected of being infected with rabies
- that they have a valid rabies vaccination certificate.

A rabies vaccination certificate is only valid if the strain of vaccine used conforms to the potency standard recognised by the WHO (2,5 international units of antigen per dose) and the animal was

Conditions for importation and validity of rabies vaccinations are determined by the importing country. The onus is on the animal's owner to determine these requirements

vaccinated at least 30 days, but not longer than 12 months prior to export to South Africa.

Alternatively, puppies under the age of three months may be vaccinated at any age after birth, but must thereafter be revaccinated at three months, and boosted according to the schedule.

In addition, animals under three months of age are considered to have valid vaccination provided their dam was vaccinated at least 30 days, but not more than 12 months prior to giving birth.

It is important to note that such animals must be vaccinated against rabies at three months of age in the Republic and the owner is obliged to then inform the South African veterinary authorities. In addition, dogs should be free of *Brucella canis*, *Trypanosoma evansi*, *Babesia gibsoni*, *Dirofilaria immitis* and *Leishmaniasis*.

The legislation governing import and export of domestic animals and wildlife is extensive and subject to continuous revision and amendment. Persons requiring further information on permits are advised to contact their nearest state veterinarian or to write directly to the Director: Veterinary Services, Private Bag X138, Pretoria 0001.

Republic of South Africa
Directorate of Veterinary Services
Identity, Rabies Vaccination and Movement Certificate for dogs and cats moving between
provinces in the Republic of South Africa

Nb: Keep this certificate as proof of vaccination.

Take it with you for revaccinations and when your dog or cat moves between provinces.

A1	Identification and description of animal:				
	Dog	Cat	Male	Female	
	Date of birth:			Colour:	
	Name of animal:			Breed:	
	Distinguishing marks:				
	Microchip number:				
A2	Owner's name:				
	Owners address:				
A3	This serves as an official vaccination certificate for interprovincial and international movements on condition that:				
	1. it accompanies the animal; 2. the property of origin is free from quarantine restrictions imposed for rabies control purposes; 3. the certificate is signed and stamped in the space below.				
A4	Vaccinations	Date	Name of vaccine	Batch No	Signature and address of veterinarian/authorised official
	Primary				
	Revaccinations				
A5	General information on Rabies Vaccination of Dogs and Cats in South Africa				
	<ul style="list-style-type: none"> All dogs and cats three months and older shall be immunised twice within a 12 month period, administered at least 30 days apart and thereafter every 3 years. Vaccination shall be carried out by an authorised person using a registered vaccine. Puppies and kittens under the age of three months can be vaccinated, provided they are revaccinated at three months and then according to the above schedule. Pregnant dogs and cats can be safely vaccinated. For international movement, some countries require a registered veterinarian to have vaccinated the animal and some stipulate annual rabies vaccinations. It is the owner's responsibility to ascertain the requirements of the importing country. 				

Fig. 8: Identity, rabies vaccination and movement certificate for dogs and cats moving between provinces in the Republic of South Africa

Rabies contact animals

Contact animals are animals that have been, or are suspected to have been, bitten or scratched by a rabid animal, or received saliva, brain or other infectious material from a rabid animal into a wound, the mouth or eyes. This includes the unweaned offspring of infected animals.

The management of contact domestic animals exposed to rabies can be complicated by the lack of an immediate perceived threat to human life. As human exposure is likely should a domestic animal develop rabies, the recommendation is normally to cull the exposed animal. Management of these cases is difficult because of emotional attachment to the animal, the value of the animal, difficulties in determining vaccination status and the democratic rights of individuals.

It is imperative that contact animals be traced, identified, safely confined and reported to the state veterinarian without delay. Failure to report such cases may subsequently result in the spread of the disease to humans or other animals. The state veterinarian will determine which contact animals pose a risk and what control measures are necessary to prevent any further spread of the disease.

Where rabies is confirmed in wild carnivores, mongooses, dogs and cats, all dogs and cats that were in close contact with the infected animal, for example those of the same household, must be euthanised under the supervision of a veterinary officer or authorised person, if they do not have a valid vaccination certificate.

Livestock known to have been bitten should be slaughtered immediately.¹⁵³ Equines must be isolated

and/or destroyed by an authorised person subject to conditions determined by the state veterinarian. Unvaccinated contact livestock including cattle, sheep, goats and horses may, in exceptional cases and subject to written permission and conditions determined by the state veterinarian, be immunised and held in isolation and close observation for six months.

Tissue and milk from a rabid animal should not be used for human or animal consumption. Meat that has been cooked and milk that has been pasteurised or refrigerated should not pose a danger. People drinking raw milk and butchering a carcass should, however, be regarded as a category 2 contact and should be vaccinated.

It is imperative that contact animals be traced, identified, confined safely and reported to the state veterinarian without delay

After taking samples from an animal with rabies or suspected of having rabies, carcasses must be burnt or buried.

A test to determine rabies antibody titre in previously vaccinated cats and dogs after an exposure to rabies occurred is available at OVI. This test can determine whether efficient antibody titres were obtained after vaccination that will protect against rabies virus infection. However this test cannot indicate whether the animal is incubating the virus.

Vaccinated dogs and cats with neutralising antibody titres exceeding of 0,5 IU/ml can be considered to have responded to vaccination, although the presence of neutralising antibodies does not guarantee protection against challenge. This result may assist in managing contact animals. It is essential that a full history is obtained and that blood samples are taken before booster vaccination (within 1–2 days post-exposure). Furthermore, the date(s) and type of contact, for example bite, scratch, and information on blood sampling and rabies vaccination(s) must be submitted with the serum samples.

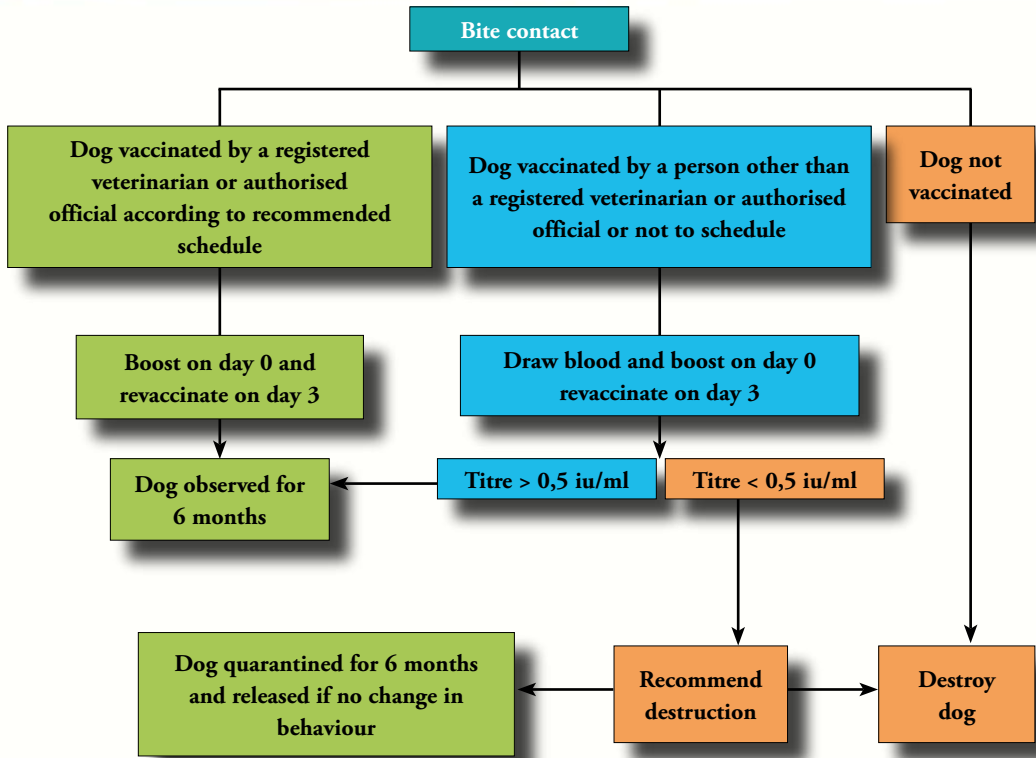


Fig. 9: Actions to be taken following bite contact with a dog

Vaccinated dogs, with antibody titres equal to or greater than 0,5 IU/ml, must be revaccinated (booster) as soon as possible after exposure (preferably within 1–2 days) and boosted three days later. The owner must be informed that there is an element of risk and if the animal shows any signs of abnormal behaviour or illness, this must immediately be reported to the state veterinarian. The animal must be confined to an adequately secure facility for six months and kept under close observation. A permit must be obtained from the state veterinarian to move the animal from the property.

Vaccinated dogs with antibody titres of less than 0,5 IU/ml, must be isolated and destroyed under the supervision of a veterinary officer or authorised person. Should the owner request that the dog not be euthanised, and the state veterinarian is of the opinion that the dog can be effectively isolated

(quarantined), he/she can authorise such isolation at a specific place in officially approved facilities under specified conditions stipulated by him/her. This course of action should only be considered under the most exceptional circumstances and the owner must be warned in writing that there is a considerable degree of risk involved and that they will be legally liable for any resultant exposure.

The animal must be effectively isolated for a six-month quarantine period. An official quarantine notice must be served by the state veterinarian on the responsible person and the conditions of quarantine conveyed in writing on an official quarantine notice. Lifting of quarantine must also be carried out in writing. During this period the animal must be under daily observation by the owner. The animal may not be released without the written approval of the state veterinarian (Fig. 10, page 54).

Quarantine facilities

This should be a well-designed and constructed, dog and cat-proof kennel/cage from which the animal cannot escape during the quarantine period. It should be of sufficient size to house the animal comfortably and hygienically. The facility should also be designed so that the animal can be properly attended and the cage cleaned with running water. This facility must be approved by a state veterinarian.

Direct contact with the animal by humans and other animals must be avoided at all costs and gloves must be worn when feeding/providing water to the animal. Officials of the veterinary department should inspect the facilities at least once a week. If the animal shows any signs of abnormal behaviour or illness, the state veterinarian must be notified immediately. All costs

resulting from quarantine are incurred at the owner's expense. Before entering quarantine, any animal with a vaccination history must be revaccinated and then boosted three days later. The vaccine must be administered within one to two days after exposure.

Animals which have had contact with rabid animals, regardless of their vaccination and immune status or type of contact, pose a risk of transmitting rabies to people and animals, should they become rabid. The conditions of quarantine and element of risk associated with this course of action, must be conveyed to the owner in writing (Fig. 10). It is recommended that all household members be vaccinated against rabies.

The presence of neutralising antibodies does not guarantee protection against rabies infection

Unfortunately adherence to the quarantine requirements does not guarantee that the animal will not subsequently develop rabies.



Director: Veterinary Services

RABIES RISK NOTIFICATION FORM AND QUARANTINE REQUIREMENTS

The risks associated with post-exposure control measures in confirmed rabies contact cases in vaccinated dogs and cats:

1. Animals which have had contact with rabid animals, and have been tested and found to have antibody levels of less than 0,5 IU/ml pose a risk of transmitting rabies to people and other animals, should they become rabid. The owner may be liable for any resultant consequences.

The reasons for insufficient immunity include the following:

- Vaccine
 - The use of expired vaccine
 - The incorrect handling, storage and transport of vaccine

- Vaccine administration
 - Incorrect dosage and route

- Animal aspects
 - Failure to develop adequate immunity (immunosuppression)
 - Poor condition or diseased when vaccinated or soon afterwards (e.g. distemper, parvo virus infection, biliary fever, internal parasites, etc)
 - Absence of antibodies (no seroconversion)

- Incompatibility of vaccine and the rabies strain

- Unreliability of vaccination history
 - Mistaken or falsified identification of animal
 - Incorrect vaccine used

- Neutralisation of vaccine by maternal antibodies

Fig. 10: Rabies risk notification form and quarantine requirements

2. Quarantine requirements

- The quarantine period for the animal shall be not less than six months
- The facility should be a well designed and constructed dog and cat-proof kennel or cage from which the animal cannot escape during the quarantine period. It should be of sufficient size to house the animal comfortably and hygienically
- The facility should be constructed in such a manner that the animal can be properly attended to and the cage cleaned with running water. This facility must be approved by a state veterinarian
- Direct contact with the animal by humans and other animals must be avoided at all costs
- Gloves must be worn when feeding/providing water to the animal
- Veterinary officials shall inspect the facilities as often as required but not less frequently than once a week
- If the animal shows any signs of abnormal behaviour or illness, the state veterinarian must be notified immediately
- All costs of the quarantine will be incurred by the owner
- All members of the family should be vaccinated against rabies according to the recommended schedule

I, the undersigned, hereby certify that I fully understand the contents and implications of this rabies risk notification form and could be held liable for any consequences arising from negligence or non-adherence to the conditions mentioned

Signed on the _____ day of _____ at _____

Signature: _____

Name: _____

Witness 1: _____ Witness 2: _____

Fig. 10: Rabies risk notification form and quarantine requirements (continued)

RABIES CONTROL STRATEGIES

It is beyond the scope of this publication to provide details of appropriate rabies control principles and strategies for all circumstances and geographic areas in South Africa. The following general principles should, however, always be considered and adapted when controlling a specific outbreak. Control strategies include quarantine, confirmation of diagnosis, determining the origin and spread of an outbreak, and specific measures to terminate transmission. The property on which the disease has presumably occurred, should immediately be placed under quarantine. This may be done by serving a quarantine notice on an individual person or, if a large area is involved, by means of a notice in the Government Gazette or printed media.

It is absolutely essential to confirm the diagnosis of rabies. Good-quality specimens must be collected. The investigating officer must submit full details of all contact animals, the date of contact and animals' vaccination status.

In the case of dogs and cats, full particulars of rabies vaccination, including the vaccination dates, type of vaccine, batch number and name of the vaccinating officer must be determined. Human contacts must be reported and referred to the relevant local health authority.

It is important to determine the possible origin of the rabies outbreak by checking whether any wild carnivores, mongooses or stray cats and dogs have recently been noticed in the area. In addition the investigating officer should establish whether animals were attacked and obtain a full history of any bite wounds inflicted. An investigation to determine whether any other animals in the area or on neighbouring farms were bitten or had contact with the suspicious vector should be performed.

All neighbours of infected farms must be notified about the disease so that they can prevent it spreading to their livestock. It is always a good idea to notify the local farmers' association or even the district agricultural union of outbreaks. In this way, inhabitants

of the entire area are alerted to the outbreak. This can also promote the state veterinary services' surveillance efforts. In urban areas the community is generally notified through newspapers, radio and television.

When an outbreak has been confirmed, the responsible state veterinarian decides on the area requiring vaccination. The general rule for urban outbreaks caused by the mongoose strain, is to vaccinate all dogs and cats in the affected street and neighbouring blocks. With farm outbreaks, animals on the infected property should be vaccinated. With outbreaks on small holdings it is important to vaccinate animals on surrounding properties.

If the outbreak is confirmed as the result of a canid strain of rabies virus, the objective must be to vaccinate all dogs and cats within the immediate surrounding area up to a radius of approximately 25 km, at the discretion of the state veterinarian.

Large-scale vaccination

This approach is the initial response to rabies outbreaks in endemic high-risk areas. The aim should be to vaccinate at least 70% of the animal population at risk in a single campaign within as short a period as possible. Where this cannot be achieved, two or more campaigns should be conducted within a year.

Cordon vaccination

The aim of cordon vaccination is to create a barrier of animal immunity. This approach has become increasingly important during the second phase of canine rabies elimination, particularly in the vicinity of international borders and national as well as provincial game reserves. This is necessary to prevent reinfection of areas currently free from rabies and to protect rabies-free wildlife areas. A cordon of 20 to 30 km is usually sufficient for this purpose.

Ring vaccination

The long-distance transport of animals, particularly dogs that may be incubating the disease, is of increasing concern to veterinary authorities attempting

to curtail the spread of rabies. This factor may result in outbreaks of canine rabies anywhere in the country at any time. It is therefore essential that immediate vaccination of the susceptible dog and cat populations be performed during the primary outbreak to prevent further exponential spread of the disease. In areas where an isolated case has been diagnosed, ring vaccination with a radius of 20 to 30 km, where at least 70% of dogs are vaccinated, has proven successful in controlling or eliminating rabies.

Door-to-door vaccination

Vaccination on a home-to-home basis is generally more expensive, resource intensive and time consuming, but coverage is invariably better. An example of the success of this approach is illustrated by a campaign in Eerstehoek, a rural district in Mpumalanga. In 1998, 20 officials vaccinated 6 498 dogs in 30 villages extending over 594 km² on a home-to-home basis. All vaccinated dogs were identified with neckbands. Almost all dogs (95,4 %) were vaccinated within seven days and the direct cost per dog vaccinated was calculated at R4,52.¹⁵⁴

Central-point vaccination

These campaigns are usually conducted at least annually in areas where rabies is endemic and the prevalence of outbreaks is high. The public are requested to bring their pets to identified venues. Accurate epidemiological information, good advertising and adequate planning are of paramount importance to ensure high coverage. Results vary from 20 to 80% and depend on the degree of attention to detail. Coverage is generally better if the campaign follows shortly after a well-publicised rabies outbreak.

Vaccination of dogs and cats on farms can be very cost-effective if combined with other activities, such as tuberculosis or brucellosis testing, or anthrax vaccination. Farmers and their workers must be informed of the vaccination activities in advance. It is important that dogs and cats belonging to workers are also vaccinated during these campaigns.

Vaccination of dogs against rabies during routine cattle-dipping activities in rural areas is relatively

inexpensive but, unfortunately, does not reach a high proportion of the dog population.

Vaccination clinics are usually held in lower-risk areas, such as formal urban areas where properties are securely fenced. These clinics operate at pre-arranged times and places. Although vaccination clinics may supplement campaigns, they cannot replace them. They primarily target animals missed during a campaign or newly-acquired puppies requiring vaccination, therefore boosting overall vaccination cover.



Plate 35: A communal dog eating an oral rabies bait

Oral vaccination

Sylvatic rabies has been successfully eradicated in Switzerland and other European countries using bait vaccine. A bait containing a live, avirulent rabies virus mutant, SAG2, has been formulated specifically for dogs and the first field trials were conducted in South Africa (G.C. Bishop 1999, unpublished data). The baits were offered to 755 dogs and more than 75% of these dogs accepted them readily. The vaccine is effective against challenge and safe for use in both target and nontarget species. Although oral rabies vaccines are not yet registered for use in South Africa, the benefits of this strategy are obvious because the handling of dogs is practically eliminated and the approach is

The aim of large-scale vaccination is to inoculate at least 70% of the animal population at risk in a single campaign within as short a period as possible

less labour-intensive than central-point vaccination. Education of communities before embarking on this course of action is imperative.

Key factors which influence success

Key factors that influence the success of control campaigns include: accurate epidemiological information, aggressive marketing, careful planning, thorough logistical preparation, intersectoral cooperation and enthusiasm.¹⁵⁵

Ideally human and dog census figures should be obtained. This may require a separate local survey. Historical information of human and animal rabies cases together with previous vaccination records for the outbreak areas are integral to the success of the entire venture. Appropriate maps indicating roads, population distribution, schools, clinics, community centres and other key community meeting points allow efficient planning of the campaign.¹⁵⁶

Cultural perceptions of local communities, level of education, attitude towards previous campaigns and awareness of rabies should be borne in mind. Cost analyses of previous campaigns and control strategies can be used to advocate for funding.

Aggressive marketing is probably the most important prerequisite for ensuring adequate coverage. This should aim at maximum mobilisation of communities by utilising all appropriate media within available resources. Television, radio, newspapers, water and electricity accounts, schools, tribal and district authorities, health authorities and clinics, churches, dip-tanks, pamphlets, posters, loudspeakers, and word of mouth are all avenues that have been successfully utilised in South Africa. Innovative measures such as advertisements placed on taxis and inserts on audio tapes distributed via the minibus association have also improved coverage. Small incentives and inexpensive gifts, such as peak hats and stickers with rabies prevention messages, have heightened awareness and promoted enthusiastic participation in vaccination campaigns.

It is important to remember that communication and marketing channels differ between communities, and it is therefore essential to identify and utilise the most locally appropriate means. The horrific nature of rabies results in extensive coverage being provided

by various media organisations and local and district authorities, usually free of charge.

Community needs and circumstances should always influence decisions on the timing and location of vaccination campaigns. A tailored strategy for each community must be well planned in advance of a campaign. Vaccination campaigns should be conducted at a time when people are available to bring their dogs. This is generally before or after normal working hours in affluent societies, in the afternoon in areas where schoolchildren are expected to bring dogs, and during weekends, particularly Saturday mornings, or school holidays in both urban and rural areas.

The choice of venue should be carefully considered. In urban areas a large open space that is well lit and preferably near shops, schools, community centres or a post office in an area of high population density, generally yields the best results.

Distances between vaccination points should not exceed 3 to 4 km. Surveys indicate that in communities lacking transport, the majority of the community will seldom walk, drag or carry their dogs beyond 2 km to be vaccinated. Where annual campaigns are held, rainfall pattern, temperature and weather conditions should be considered if high vaccination coverage is to be obtained.

Ensure that adequate supplies of vaccine, certificates, and clean sterile syringes and needles are available. Sufficient tables, chairs and assistants are vital for a smooth-running and efficient campaign. Ensure that all administrative material and equipment are available before initiating the campaign. These include the items on the campaign equipment checklist (Table 13).

The type of operation chosen will determine the scale of interdepartmental liaison and intersectoral collaboration between the Departments of Health, Justice, Education and the South African Police Service required. It is important that tribal authorities, organised agriculture, local government, private veterinarians and welfare organisations must be involved to ensure success.

The success of any disease control programme is directly related to the enthusiasm and commitment of team leaders and members. The decision on

TABLE 13: Campaign equipment checklist

Veterinary	Stationery	General	Marketing
Vaccine	Certificate books	Cooler box	Banners
Syringes	Pens	Ice packs	Posters
Needles	Official stamps	Trunks	Direction boards
Stericaps	Clipboards	Soap	Loudspeaker
Veterinary medicines		Water	
Medical aid kit		Towels	
Protective clothing		Umbrella	
Restraining equipment		Mobile telephone	
Forceps		Tables and chairs	
		Gas stove	
		Pots for sterilising equipment	

appointing campaign leaders should therefore be carefully considered.

Excellent results are usually obtained where “operational headquarters” are established and team members fully briefed on campaign objectives and background rabies epidemiology. Team members should be well orientated to local circumstances and cultural practices, and be supplied with all the necessary equipment prior to the initiation of the campaign. Full briefing and regular reporting must continue throughout the campaign. During rabies vaccination campaigns, issuing of vaccination certificates is optional and at an owner’s request.

Rabies vaccine is generally available at all private veterinary practices and state veterinary offices throughout South Africa. Owners of dogs and cats can also purchase rabies vaccine through pharmaceutical companies and pharmacists.

Post-vaccination surveillance for outbreaks is a fundamental requirement of any rabies control programme. The efficiency of vaccination campaigns is generally evaluated by the impact on rabies incidence in target and nontarget species. Ongoing surveillance is required to detect residual foci or reinfection of areas where rabies has been eliminated. Campaigns should be carefully analysed for coverage, efficiency, cost effectiveness and lessons learnt.

It is important to remember that communication and marketing channels differ between communities and it is therefore essential to identify and utilise the most locally appropriate means

Additional measures enhancing rabies control programmes

Enforcement of registration or licensing of all dogs and cats may enhance rabies control programmes, as vaccination is an essential prerequisite to licensing. A fee is frequently charged for a licence and revenues collected may be used to maintain rabies control programmes.



Plate 36: Maintaining high visibility and befriending communities are two very important aspects in rabies control and prevention

“Spot fines”, admission of guilt citations and prosecution of owners for violating control regulations, including the failure to vaccinate or licence their animals and failure to obtain or present a “proof of vaccination” certificate during interprovincial movements, may be used in extreme cases to ensure rabies control.

All communities should be encouraged to control stray animals and sterilisation programmes should be promoted.



Plate 37: Central vaccination points must be carefully selected and easily accessible. Promotional T-shirts and caps are being worn by this group

A good knowledge of local dog ecology (dog numbers, turnover rates, reasons for ownership, other diseases, housing) is crucial when planning control measures

Rabies vaccines may be used in young puppies, which must be boosted at three months of age and again within the following year. Revaccination must be performed every three years thereafter



Plate 38: Dogs may be vaccinated intramuscularly or subcutaneously with rabies vaccine



Plate 39: Cats must also be vaccinated against rabies in South Africa



Plate 40: The target species in canine rabies endemic areas. The objective should be to vaccinate a high proportion of the dog population in order to create a large group of rabies-immune, mature and healthy dogs

FREQUENTLY ASKED QUESTIONS

- How often must I vaccinate my dog? See page 47, 48
- My child was bitten by a mouse (shrew, rat, or monkey). Must he or she receive antirabies treatment? Page 34, 36
- Must I have my cat vaccinated against rabies? See page 47, 48
- I have been bitten by a dog. The dog is very aggressive and frequently bites people. What must I do? Page 36, 37, 41
- I was bitten by a rabid dog two weeks ago and I was given rabies vaccine within a day of the incident but no RIG was administered. What must I do now?Page 38—40
- I was bitten by a rabid dog four days ago and I was given rabies vaccine within a day of the incident but no RIG was administered. What must I do now?Page 38—41
- My farm staff dug up the carcass of a rabies positive cow that had been buried a day ago. The staff then consumed the meat of this carcass. What must be done now? Page 33
- We have been drinking the milk of a rabid cow up to the day she was destroyed. What should be done? Page 51
- What is the earliest age that I may vaccinate my puppy or kitten for rabies? Page 47, 48
- Is it safe to give rabies vaccine at the same time as other dog vaccines, e.g. distemper, parvo and hepatitis? Page 48
- What side-effects will rabies vaccination have on my animal? Page 47, 48
- One of my dogs is positive for rabies. What should I do about my other animals? Page 51—55
- How soon after vaccination are my dogs protected against rabies? Page 47
- Should wild animals which are kept as pets be vaccinated against rabies? Page 48
- My cow was positive for rabies. What must I do about this cow's calf and the other cattle that were in contact with this cow? Page 51
- My dog and cat were vaccinated during a rabies campaign. However, I do not have any documentary proof that vaccination was done. Should there be contact with rabid animals, what is their vaccination status? Page 51, 52
- Can rabies be transmitted between people? ... Page 33
- I was bitten by a mongoose two weeks ago. What should I do? Page 36, 41
- Can birds contract rabies? Page 34
- What part do bats play in rabies transmission in South Africa? Page 3, 11
- Can clinical rabies in humans be treated? Page 44

EXPERT ADVICE ON RABIES IS AVAILABLE FROM:

Allerton Provincial Veterinary Laboratory
Tel: 033 347 6200/6247

ARC-Onderstepoort Veterinary Institute, Rabies Unit
Tel: 012 529 9440/420/439

**National Institute for Communicable Diseases
of the National Health Laboratory Service**
For laboratory related queries, Tel: 011 386 6339
For advice on prophylaxis and medical issues, 24 hour Hotline: 082 883 9920

Department of Agriculture, Directorate Veterinary Services
Tel: 012 319 7456

National Bioproduct Institute, South Africa (for rabies immunoglobulin)
Office hours
Tel: 031 719 6715, 031 719 6704
24 Hour Emergency line: 082 320 3306

RABIES EDUCATIONAL VIDEOS

for health workers, schools and the community are available from:

Tel: 033 347 6264

USEFUL LINKS

Find useful information regarding rabies from these websites:

Centers for Disease Control and Prevention: www.cdc.gov

World Health Organization: www.who.org

World Rabies Day: www.worldrabiesday.org

Southern and Eastern Africa Rabies Group: www.searg.info/

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There is a clear mandate for children to be formally educated on rabies transmission, the disease and prevention, particularly as education interventions have been shown to reduce the number of dog bites in children

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All persons judged to be at risk for rabies exposure must receive rabies prophylaxis as soon as possible, even when there was a delay in presentation to a health service

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APPENDIX 1

Laboratory diagnosis of rabies in humans

(Tests available at National Institute for Communicable Diseases at the time of press)

Specimen	Transport of Specimen*	Laboratory Procedure	Sensitivity/interpretation of Results	Comments
Saliva	Plastic, screw top specimen jar/tube (need at least 200 µl)	RT-PCR Virus isolation	Sensitive, but negative result <u>does not</u> exclude rabies virus infection Sensitive, but is time-consuming	<u>Only</u> patients with suspected rabies disease. <u>Saliva</u> specimens are preferred for ante mortem diagnosis. No sputum specimens. Isolation of rabies virus may confirm other diagnostic tests
Nuchal biopsy	Two dermatological punches collected from the nape of neck: <ul style="list-style-type: none"> • 1 fresh on saline-wetted gauze in screw-top jar • 1 in formalin 	RT-PCR and histology	Specimens are usually positive from day 1 of onset of clinical disease. Sensitive, but negative result does not exclude rabies virus infection	Only patients with suspected rabies disease. Saliva specimens are preferred for ante mortem diagnosis. Specimen must include hair (virus is deposited in nerves around the hair follicles)
Nuchal biopsy	Plastic, screw top specimen jar/tube (need at least 200 µl)	RT-PCR Fluorescent antibody test	Sensitive, but negative result <u>does not</u> exclude rabies virus infection Sensitivity depends when the sample was collected (sero-conversion time differs from patient to patient; sequential samples must be sent and may only be positive after 5 days of disease). A negative result <u>does not</u> exclude rabies virus infection	<u>Only</u> patients with suspected rabies disease. <u>Saliva</u> specimens are preferred for ante mortem diagnosis <u>Only</u> patients with suspected rabies disease. Diagnostic since serum antibody induced upon vaccination does not cross the blood-brain barrier
Serum	Clotted blood tubes (need at least 200 µl)	Fluorescent antibody test	As for CSF	Diagnostic in unvaccinated patients. Also for determination antibody titer upon vaccination
Brain	Half in 50 % glycerol saline** and half in 10% neutral buffered formalin**. In screw top jars***	Fluorescent antibody test Virus isolation	Gold standard for rabies diagnosis with a sensitivity of more than 99% 99% agreement with FAT results	Entire brain (in two halves) or cubes of different sections of brain. Confirmatory test for fluorescent antibody test

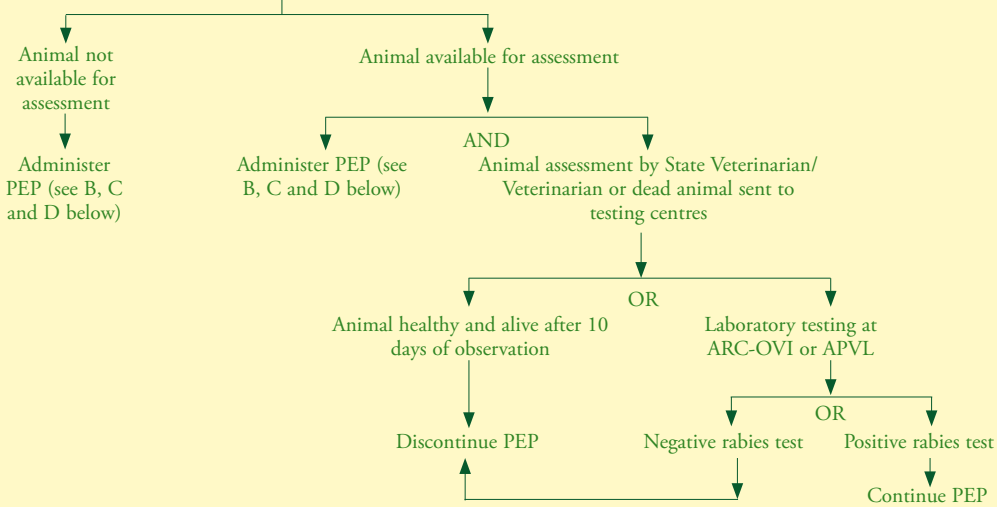
* Transportation: wrap specimen jar/tube in absorbent material and place in a sturdy container. Place in secondary container (i.e. courier boxes/bags) and transport at 4 °C (cooler with frozen ice packs) to reach the laboratory as soon as possible. Apply necessary warnings for bio-hazardous/infectious materials to the package.

** 50 % glycerol saline is prepared by adding an equal volume of glycerol to an equal volume of saline (for example 50 ml glycerol and 50 ml saline); 10% neutral buffered formalin is prepared by adding 1/10th volume of formalin to buffer (for example 10 ml formalin and 90 ml buffer).

*** If brain cannot be preserved in glycerol saline/formalin, the brain may be frozen fresh and shipped on dry ice (or as cold as possible) to reach the laboratory ASAP. Warning: sample may degrade and influence outcome of testing.

APPENDIX 2

1. Assess the risk of transmission (page 36) and category of exposure (see B below)
2. Record full details and history of the incident
3. If risk of rabies is considered, proceed as indicated in the flow chart



A. Animal Assessment

The following aspects must be considered:

1. Vaccination: tangible proof of current rabies vaccination status (dog or cat) must be obtained. See constraints on page 36
2. Behavioural changes: all aspects must be considered
3. Possible exposure: any known incident during the previous few months
4. Rabies endemicity: entire RSA is rabies endemic but current incidence and prevalence are important
5. Provocation: was the animal's reaction due to provocation?
6. Stray (unsupervised animals): this history may be unreliable

B. Categories of rabies exposure

Risk Cat.	Type of exposure	Action to be taken
1	Touching/feeding animal Licking of intact skin	None if case history is reliable If history is not reliable, treat as for category 2
2	Nibbling of uncovered skin Superficial scratch without bleeding	Apply wound treatment Administer vaccine Do not administer antirabies immunoglobulin Stop vaccination if animal is rabies negative on laboratory test, or remains healthy after 10 days observation
3	Bites/scratches which penetrate the skin and draw blood Licking of mucous membranes or broken skin	Apply wound treatment Administer vaccine Administer antirabies immunoglobulin Stop vaccination if animal is rabies negative on laboratory test, or remains healthy after 10 days observation

C. Wound treatment

1. Flush well with soap and water or water alone for at least 5 minutes and apply disinfectant eg. 70% alcohol or iodine solution (eg. Betadine)
2. Avoid suturing or use of compressive bandages
3. Administer anti-tetanus treatment and antibiotics if indicated

D. PEP schedules

No previous immunization

Category 2: Inject single dose vaccine into deltoid muscle (NEVER in gluteus) or antero-lateral thigh in children on days 0, 3, 7, 14 and 28

Category 3: Infiltrate immunoglobulin (20 IU/kg) on day 0 into and around wound, with remainder into deltoid of opposite arm to vaccine. Inject vaccine as for category 2. Rabies immunoglobulin if not immediately available can be given up to 7 days of the first vaccine dose, but never after 7 days

Previously immunized

Category 2 and 3 exposures: Inject single dose vaccine into deltoid muscle on days 0 and 3. No rabies immunoglobulin should be given

Special considerations

Late presentation: Treat without delay as if the contact occurred recently, following the guidelines for wound treatment (where possible), and administration of immunoglobulin and vaccine. Deviation from the suggested doses/regimens is not advised.

Immunosuppressed patient: Emphasize thorough wound cleaning and ALWAYS administer antirabies immunoglobulin in both category 2 and 3 exposures in addition to the vaccine. Deviation from the number of doses and prescribed regimens is not advised.

Bat exposures: PEP provides variable protection against rabies-related viruses. The categories of exposure do not apply to bats, as transmission can occur with very minor or even inapparent contact. Any close contact with bats is considered as a category 3 exposure.

Fig. 7: Actions following a human exposure to a suspected rabid animal

FOR FURTHER
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ARC-Onderstepoort Veterinary
Institute, Rabies Unit
(OIE Regional Rabies Reference
Centre for Southern and
Eastern Africa)
Tel: 012 529 9440/
012 529 9420/
012 529 9439

National Institute for
Communicable Diseases
For laboratory related queries,
Tel: 011 386 6339
*For advice on prophylaxis and
medical issues,*
Hotline: 082 883 9920

Department of Agriculture,
Directorate Veterinary Services
Tel: 012 319 7456

National Bioproduct Institute,
South Africa (for rabies
immunoglobulin)
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