

Human Rabies: A tragedy that must be prevented

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Abstract

Human rabies is endemic throughout South Africa and every year a number of deaths occur, mainly in children, largely due to bites from infected dogs, coupled to incorrect management after the exposure. The encephalomyelitis that follows central nervous system invasion by the rabies lyssavirus is invariably fatal. However, modern vaccines and immunoglobulin registered for use in South Africa are safe and very effective in preventing rabies when administered correctly before and after exposure. Unfortunately the prohibitive cost of rabies vaccine does not allow for

prophylactic routine immunisation of all children or indeed for the immunisation of all animal bite victims in South Africa. This article reviews current best practice in determining which persons should receive pre-exposure vaccination and post-exposure treatment. It updates and expands the clinical guidelines for rabies management prepared by the South Africa Department of Health, briefly discussing specific principles of management. In addition, the confirmation of diagnosis and approach to patient care are described.

Introduction

Rabies continues to exact an enormous toll on human life with the World Health Organization estimating more than 35 000 annual deaths due to rabies

world-wide¹. More than 99% of all human rabies deaths occur in the poorest developing countries, particularly India². The re-emerging status of rabies

in Africa is of concern. This trend has been attributed to population growth with parallel accelerated dog population growth, mobility of human populations,

particularly refugees, high rates of urbanisation and a disintegration of rabies control in domestic animals and reemergence of wildlife reservoirs^{3,4}.

The rabies virus is almost exclusively transmitted in the saliva of infected animals and has the highest case fatality rate of any known human infection. Once the virus enters the central nervous system of the host, the resulting encephalomyelitis is almost invariably fatal. Fortunately the availability of safe and effective vaccines and immunoglobulin has prevented many fatalities and almost 10 million people receive post-exposure treatment annually after potential rabies exposure, mostly following dog bites.

DISTRIBUTION OF RABIES IN SOUTH AFRICA

Rabies is endemic throughout South Africa, except in the Kruger National Park where it is yet to be diagnosed in

wildlife although individual stray rabid dogs have been confirmed⁵. The map reflects the distribution of maintenance animal hosts (Figure 1). Initially most human rabies in South Africa resulted from mongoose bites in the central plateau areas. However, with the introduction of canid virus into the Northern Province in the 1940's and KwaZulu/Natal in the 1960's, dogs became the most important source of human infection. In recent years, the vast majority of South African human rabies cases have followed bites from infected dogs in KwaZulu/Natal⁶. From 1989 -1999 inclusive, 156 of the 172 humans diagnosed with rabies, lived in KwaZulu/Natal. However, dog and human rabies surveillance has deteriorated in some parts of South Africa and the situation may be worse in certain provinces than reflected by official notifications. Recently, most South African victims have been children under the age of ten years. The reasons

why children are more vulnerable include their relatively short height, inquisitive nature, attraction to animals, and inability to protect themselves when attacked by the animals.

MANAGEMENT OF HUMANS FOLLOWING POTENTIAL EXPOSURE

Although other mechanisms have resulted in rabies transmission, including the deposit of infected saliva on mucous membranes, transplant of infected corneal grafts and aerosol transmission of the virus in laboratories, practically all human rabies cases follow viral inoculation through the skin by the bite of an infected mammal^{7,8}. The rabies virus is intermittently present in the saliva of the affected animal during clinical disease and occasionally for a number of days prior to the onset of disease⁹. The success of transmission depends on a number of factors, particularly the number of bites, depth of bites and their location on the body. Record reviews of untreated human cases suggest that 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 clothing¹⁰. As early correct management is effective in preventing human rabies, it is essential to correct the deficiencies identified in the approach of South African clinicians towards managing suspected rabies exposures¹¹.

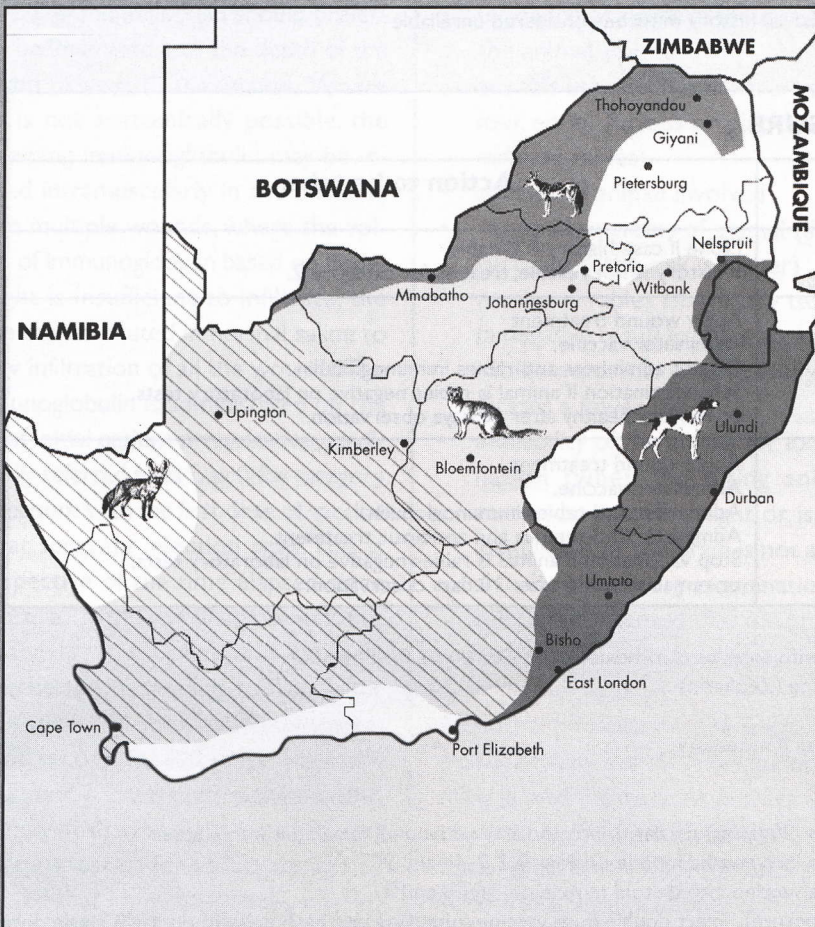
The management of rabies in humans following exposure, (Figure 2) includes the following strategies:

- a. Wound treatment
- b. Anti-rabies immunoglobulin
- c. Human rabies vaccination

Wound treatment

The bite wound should be thoroughly cleaned as soon as possible, using clean water. If only environmental water is available at the time of the bite, this should be used without delay to wash saliva from the skin and wound. When the patient presents to medical care,

Figure 1: Map of the distribution of animal hosts for rabies in South Africa.



Source: Department of Health. Clinical guidelines for Rabies management.

more thorough washing can be done. In this situation, standard wound care to reduce the chances of bacterial infection should be initiated by copious flushing, for five to ten minutes, with normal saline or a 1:20 dilution of 5% chlorhexidine in the water. Irrigation of deep puncture wounds, e.g. following a feline bite, is improved by using a syringe. Bleeding should be encouraged and wound suturing should preferably be avoided or delayed¹². Applying an iodine-based disinfectant or 70% alcohol to the wound after flushing is also indicated, as these chemicals destroy the rabies virus¹³.

Anti-rabies immunoglobulin

Anti-rabies immunoglobulin is produced from human plasma containing high anti-rabies titres and treated to kill any serum-borne viruses. It is safe and provides rapid passive immunity that has a half-life of approximately three weeks. The dosage is 20 International Units (IU) per kg body-mass¹⁴. The complete dose of immunoglobulin should preferably be infiltrated into the depth of the wound or next to the wound. Where this is not anatomically possible, the remaining immunoglobulin may be injected intramuscularly in the buttock. With multiple wounds, where the volume of immunoglobulin based on body-weight is insufficient to infiltrate, the dose can be diluted in normal saline to allow infiltration of all the wounds. The immunoglobulin is administered on the day of initial patient presentation, traditionally referred to as Day 0, for category 3 exposure with the first dose of vaccine but at separate injection sites. This is irrespective of the time elapsed since exposure¹⁵. If the immunoglobulin is not available when vaccination is initiated, it may be administered up to Day 7 after vaccination. However, its administration is not recommended prior to vaccination, nor is it currently recommended for individuals who have received pre-exposure vaccination as it is commonly believed that immuno-globulin may interfere with the rapid anamnestic response to vaccine.

Human rabies vaccination

It is imperative that vaccination be instituted as soon as possible after exposure to the rabies virus, even before there is laboratory confirmation of animal diagnosis. Ideally, post-exposure treatment would be administered to all bite victims but in many countries, including South Africa, treatment is performed at the expense of the Department of Health and current vaccine prices preclude this approach. In South Africa, post-exposure treatment is provided to individuals at high risk of rabies infection but any individuals in the low risk category concerned for their own safety are encouraged to receive the vaccination at their own expense.

Judging whether post-exposure treatment is necessary, should include an estimate of risk, based on the following criteria, with high-risk exposure necessitating vaccination¹⁶:

- type of contact (see Figure 2)
- incidence of rabies in the district of the animal source
- animal's behaviour (abnormal behaviour, either furious or placid, could indicate rabies)
- species of animal involved
- vaccination status of animal (if not vaccinated, the risk is higher)
- results of rabies laboratory testing (a negative result from an approved rabies veterinary laboratory indicates a lower risk)
- availability of the animal for examination (when the biting animal cannot be traced, caught or is unidentifiable, or the brain is not available for laboratory examination, it should be assumed that the animal was rabid).

Abnormal behaviour in the animal and type of contact are the most important criteria and Figure 2 emphasizes the importance of close liaison with the state veterinarian when decisions are made. If a family practitioner is in doubt, the patient who has been bitten should be vaccinated. In addition, Section 45

of the Health Act (No 63 of 1977) makes it mandatory that any human exposed to a confirmed rabid animal, as well as subsequent illness or death must be reported to the Department of Health immediately.

Post-exposure rabies vaccine induces immunity after a delay of 7-10 days. The cell-culture vaccines currently registered for use in South Africa, namely human diploid cell vaccine (HDCV) and purified Vero-cell rabies vaccine (PVCV), meet the WHO potency standard of greater than or equal to 2.5 IU per dose, and are inactivated, highly purified and safe. Adverse effects are uncommon and severe reactions are exceedingly rare with these vaccines¹⁷. They have been used extensively in pregnancy, with excellent results¹⁸.

All persons judged to be at high-risk of rabies exposure should be vaccinated, with treatment initiated as soon as possible, even if there has been a delay in presentation. Although all treatment schedules presented in Table 1 (overleaf) are included in the most recent WHO recommendations and are valid for the cell-culture vaccines registered in South Africa, the Essen schedule remains the standard approach. The abbreviated 2-1-1 Zagreb intramuscular regimen is usually only advocated for use in risk category 2 (not category 3) exposure victims. Although the intradermal schedules (Oxford and Thai Red Cross) have proven effectiveness they should not be used in immunocompromised individuals, or those using chloroquine anti-malarial drugs. A poorer response has been recorded in these groups¹⁹.

The Essen schedule of vaccination may be used in all types of exposure requiring immunisation. A single dose of vaccine is administered intra-muscularly into the deltoid of adults or into the anterolateral thigh of infants or children under one year of age on Days 0, 3, 7, 14 and 28 of treatment. It is important to note that the vaccine should not be

Table 1: WHO Approved Post Exposure Rabies Vaccination Regimens

Regimen	Schedule						Vials/Visits
	Day	0	3	7	14	28	
1. Essen (IM X5) Dose: One dose (1.0 or 0.5 ml*) into deltoid	Day	0	3	7	14	28	5/5
2. Zagreb (IM 2-0-1-1) Dose: One dose (1.0 or 0.5 ml*) into deltoid	Day Sites	0 X2		7 X1		21 X1	4/3
3. Thai Red Cross (ID 2-2-2-0-1-1) Dose: One dose (0.1 ml HDCV) per site intradermally	Day Sites	0 X2	3 X2	7 X2		28 X1 90 X1	1-2/5
4. Oxford (ID 8-0-4-0-1-1) Dose: One dose (0.1 ml HDCV) per site intradermally	Day Sites	0 X8		7 X4		28 X1 90 X1	2-3/4

* The recommended dose of vaccine is present in 0.5 ml of PVCV or 1.0 ml of HDCV

injected into the buttock as fat depots may interfere with vaccine uptake. Some authorities advocate giving a single dose in both deltoids on Day 0, i.e. doubling the first dose of vaccine, in a number of circumstances, including situations where there has been a delay of 48 hours or more in starting treatment; anti-rabies immunoglobulin was administered before the first dose of vaccine; underlying chronic medical conditions such as cirrhosis exist, or bite-victims are using chloroquine¹⁰. Persons who have received pre-exposure vaccination should receive only two booster doses of vaccine on Days 0 and 3.

The two cell-culture vaccines available in South Africa can be used interchangeably and it is essential that the Cold Chain be maintained between 2 and 8°C during all handling and storage of the vaccine and immunoglobulin. Following the reconstitution of the rabies vaccine, it must be used on the same day and the remaining vaccine discarded at the end of the day. The vaccination schedule may be discontinued if the suspected source animal remains healthy for 10 days after the exposure or if the brain specimen from an euthanased animal is reported negative by an approved veterinary laboratory¹⁶.

Prevention of tetanus and other bacterial infections

A detailed discussion of the merits and indications for prophylactic antibiotics

is beyond the scope of this article and this topic has been reviewed elsewhere^{12,20}. A forthcoming article in this series will deal with tetanus in depth, but it is usually advisable to administer a booster dose of tetanus toxoid (TT) adsorbed vaccine (0.5 ml intramuscular) at the time of wound treatment in individuals who have completed a primary course.

DIAGNOSING HUMAN RABIES

Clinical picture

The incubation period of human rabies is highly variable but seldom exceeds 90 days (usually between 2 and 8 weeks). Non-specific prodromal symptoms last for one to four days and include fever, headache, malaise and non-specific gastrointestinal symptoms. Neuropsychiatric symptoms, including irritability, depression, anxiety and insomnia, may be present and sensory symptoms, including pruritis and pain at the bite site, which has healed, are commonly experienced. An acute agitated phase (furious form) usually follows and is characterised by speech

and psychomotor hyperactivity, including episodic terror and manic behaviour, or generalised convulsions that may be triggered by various sensory stimuli.

As the disease progresses, there is inexorable loss of neurological function, with dysphagia, dysarthria, spasms of the involuntary musculature and hyper-salivation with resultant classical hydrophobia, or fear of water²¹. Aerophobia (fear of air), facial grimacing and an exaggerated response following exposure to air movement on the face, is another typical symptom which should be sought by the family practitioner blowing on or fanning the patient's face. Convulsions and muscular spasms become prominent as the patient's mental state deteriorates with progressive disorientation, hallucinations, confusion and coma. Patients succumb within two weeks of disease onset due to progressive cardio-respiratory failure, often preceded by obvious central nervous system respiratory irregularity. In addition, other systemic features may be present including arrhythmias and ventilation perfusion imbalances^{22,23}.

Table 2: Differential diagnosis of rabies in humans (after Warrell, DA)²⁴

FURIOUS RABIES	PARALYTIC RABIES
Hysterical pseudo hydrophobia	Post-vaccinal encephalomyelitis
Tetanus	Poliomyelitis
Encephalitides, including other viral infections	Guillain Barre syndrome and other causes of Landry-type ascending paralysis
Delirium tremens	
Various chemical intoxications	

Occasionally the agitated phase is absent and progressive paralysis due to spinal cord affection is the prominent feature (dumb form). Table 2 shows the differential diagnosis of human rabies²⁴.

Confirming the diagnosis

A history of contact with an animal proven to be rabid makes the diagnosis more secure. Currently, no laboratory test exists to diagnose rabies during the incubation period, and even after the onset of clinical signs or death, laboratory diagnosis is not simple, and false negative results frequently attend most diagnostic tests. It is, therefore, often necessary to perform complementary tests on different specimens or even to repeat the same tests. The most commonly utilized test for ante-mortem diagnosis is detection of antigen by fluorescent antibody testing in corneal impression smears or nuchal skin biopsies²⁵. All human specimens for rabies diagnosis in South Africa should be submitted to the National Institute for Virology, where there is considerable expertise in rabies diagnosis. The ante-mortem diagnosis of rabies has been greatly facilitated by the availability of a PCR test that can be performed on cerebrospinal fluid²⁶.

If diagnosis is not confirmed prior to death, then post-mortem diagnosis should be made as human rabies may be considered an unnatural cause of death (Inquest Act - No. 58 of 1959). It is essential that the medical practitioner performing the autopsy is vaccinated against rabies and takes careful infection control precautions, including wearing an impervious gown and apron, gloves and a visor when obtaining specimens²⁷. Ideal post-mortem brain specimens include small cubes (1-2 cm) of cerebrum, cerebellum, hippocampus, medulla, thalamus and brain stem, preserved separately in 50% glycerol-saline and 10% buffered neutral formalin in sealed screw top jars for virological and histological examination, respectively. Careful labelling and packaging in secure, rigid secondary, and where possible tertiary, containers

full of absorbent material (paper or sawdust) and direct communication with the National Institute of Virology are essential before the specimens are dispatched by courier.

TREATING CLINICAL HUMAN RABIES

The almost universally futile nature of clinical human rabies treatment makes it imperative that relatives of the victim be honestly counselled early as to the extremely poor prognosis. Every effort must be made to ensure the patient's comfort with adequate sedation, while careful supportive care, including maintenance of nutrition, and correction of fluid-electrolyte and acid-base balances, should be provided, preferably in an intensive care unit. Although life-support measures may prolong the clinical course of disease, they are unlikely to result in survival, except on very rare occasions^{23,28,29}. Currently available anti-viral drugs and corticosteroids have no proven benefit.³⁰

Intensive nursing care by volunteer staff, fully immunised against rabies, may limit complications such as aspiration. Infection control precautions are important for these health workers 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, and wearing respiratory protection while limiting the movement of the patient³¹). If a staff member is exposed to potentially contaminated secretions, e.g. patient saliva contamination of a mucous membrane, they should immediately receive post-exposure treatment, by copious flushing with clean water and vaccination according to their vaccination status.

PRE-EXPOSURE HUMAN RABIES PROPHYLAXIS

A recent review found that at current human rabies vaccine prices, routine

use of pre-exposure vaccination is generally not cost effective³². 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 pre-exposure prophylaxis is performed at the expense of vaccine recipients or their employers.

The pre-exposure vaccination involves administration of a total of 3 doses of rabies vaccine (either HDCV or PVCV) on Days 0, 7 and 28 (or Day 21). The antibody response requires approximately 7-10 days to develop and usually persists for at least 2 years. Single booster doses can either be routinely administered every 1 to 3 years depending on the perceived risk of rabies exposure or on the basis of demonstrating waning of serum virus-neutralising antibody levels to below 0,5 IU/ml. Although the intradermal route is generally considered acceptable for pre-exposure vaccination, intramuscular HDCV has provided higher levels of neutralising serum antibody at two years postvaccination³³. The intramuscular route should be used whenever the vaccine recipient is taking chloroquine or is immunocompromised^{34,35}.

The following groups of people deserve special mention regarding pre-exposure human rabies prophylaxis:

High risk occupational groups

People with increased occupational risk of exposure to infection, such as veterinary staff, wildlife handlers, plague surveillance teams, laboratory personnel working with rabies virus or animal welfare staff, should receive pre-exposure prophylaxis.

Children in rabies-endemic areas

Simultaneous administration of purified rabies Vero cell vaccine with diphtheria, tetanus, whole-cell pertussis and inactivated poliomyelitis vaccine at 2, 3 and 4 months, has resulted in all infants developing protective antibody concentrations against all five diseases with

no serious adverse effects³⁶. 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.³⁷

Travellers to rabies-endemic areas

Rabies is one of the diseases of importance to the burgeoning community travelling to developing countries, particularly in the back-packing or adventure category. In certain areas there is frequent tourist exposure to dogs, e.g. 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 licks³⁸. Unfortunately discussion on reducing rabies risk is one of the topics often neglected by travel medicine advisors during pre-travel consultations³⁹.

Travellers to rabies-endemic areas must be educated on their risk of rabies exposure and local reservoir species so that they can avoid contact with potentially rabid animals. They should also receive instruction on correct wound cleaning procedures, and the availability and importance of correct post-exposure treatment with vaccine and immunoglobulin at their destination. Travellers with potential occupational exposure or long-term expatriate residents in high-risk areas, particularly those living in close proximity to the local population and their dogs, should certainly receive pre-exposure vaccination⁴⁰. In addition, for other travellers advice and vaccination should be tailored to take into account the area to be visited, local rabies epidemiology, availability of quality medical care, safe vaccines and immunoglobulin, mode of travel, potential degree of exposure and underlying medical conditions or medication.

CONCLUSION

The death of a human from rabies should be viewed as a tragedy that could have been prevented. The tools

available to us are highly effective in preventing rabies. These include the vaccination of dogs against rabies, effective management of dogs, particularly strays in urban and rural areas, the provision of prophylactic rabies vaccination for individuals at high risk of exposure because of their occupation or travel, and correct management after exposure to a potentially rabid animal. Family practitioners must ensure that wound management, risk assessment and administration of vaccine and immunoglobulin are correctly performed because the costs of neglect are enormous.

A TRIBUTE TO GEORGE BISHOP

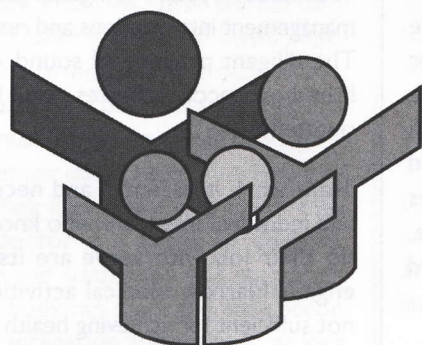
This article is dedicated to the memory of our friend and colleague, George Bishop who unexpectedly passed away on 25 August 2001. His keen intellect, wonderful sense of humour, meticulous laboratory and field work, passion for controlling rabies and warm friendship will be sorely missed. George's deepest desire would have been to see this article contribute to the prevention of any further human rabies deaths in South Africa.

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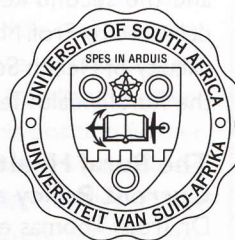
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