Rabies

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EPIDEMIOLOGY

RABV is widely distributed around the world. Territories reported to be free of the virus are mainly islands and peninsulas. These include Great Britain, Ireland, Iceland, Sweden, Norway (apart from the Svalbard Islands to the north of the mainland), Denmark, Portugal, Spain, Gibraltar, Malta, Albania, Cyprus, Bahrain, Oman, Qatar, United Arab Emirates, Hong Kong, the Malaysian peninsula, Singapore, certain Indonesian and Philippine islands, Republic of Korea, Japan, Australia, New Zealand, Fiji, Hawaii and certain other western Pacific and Caribbean islands, Libya, Cape Verde, Sao Tome, Comores, Mauritius and Antarctica, but several of the countries mentioned in the Persian Gulf and South East Asia occasionally experience re-introductions of the disease. Several countries in western Europe have eradicated RABV as a result of successful oral vaccination campaigns in fox populations, but have nevertheless reported the presence of bat-associated lyssaviruses. In 1996, European bat lyssavirus 2 was also found in a bat in Britain, hitherto considered to be free of lyssaviruses. Apart from rare imported cases of the disease, Australia has always been free of RABV but ABLV has been recognized in fruit bats (flying foxes) as well as in insectivorous bats, and since November 1996, three people have died as a result of ABLV infection after being bitten or scratched by bats.
The distribution of rabies in South Africa by major host species. From Rabies Guide for the Medical, Veterinary and Allied Professions, 2nd edition (2010). Reproduced with permission from the Directorate Animal Health, Department of Agriculture, Forestry and Fisheries

Rabies was diagnosed for the first time on the African continent during an outbreak in dogs in the Eastern Cape Province of South Africa in 1893, although historical writings suggest that suspected rabies cases had previously occurred in that country some time prior to this, in dogs and in humans. The virus in dogs was apparently eradicated by August 1894 through muzzling, restriction of dog movements, and the destruction of stray animals, as rabies was not confirmed again in South Africa for 34 years after this. During this time however, there was mounting anecdotal evidence of an endemic form of the disease in small wild carnivores, including genets (Genetta genetta) and yellow mongooses (Cynictis penicillata). The disease was confirmed in 1928 in two children bitten by a yellow mongoose in the North-West Province, and since that time rabies has been diagnosed regularly in South Africa. Elsewhere in southern Africa, sporadic outbreaks of the disease occurred in the first half of the 20th century. Then, in 1947 a large outbreak of dog rabies originated in northern Namibia, sweeping south and east across the continent to reach Botswana, Zimbabwe and the Limpopo Province of South Africa by 1950. From here, the disease crossed into central Mozambique in 1952 and entered Swaziland in 1954. In 1961, dog rabies spread from the Maputo district in southern Mozambique into northern KwaZulu-Natal in South Africa. Apart from unconfirmed reports of the disease in the nineteenth century, KwaZulu-Natal had hitherto been free of rabies, and the epidemic which followed the introduction of the virus in 1961 was of an intensity unprecedented in South Africa. Vigorous efforts were made to control the disease through the vaccination of dogs and the prohibition of translocation of unvaccinated individuals, and these led to the outbreak in KwaZulu-
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Natal being finally brought to an end late in 1968. Rabies reappeared in the northern districts of KwaZulu-Natal, adjacent to the Maputo district of Mozambique, in 1976 at a time when there was an influx of refugees fleeing the unsettled conditions that followed the assumption of independence by Mozambique from Portugal. After its re-introduction into Kwazulu-Natal in 1976, dog rabies proved to be intractable. Currently, the entire South Africa is considered endemic for rabies, with a focus in dogs in Kwazulu-Natal extending into the Eastern Cape and Mpumalanga provinces, and outbreaks seen in Limpopo and Gauteng provinces.

Although all mammals are susceptible to infection with RABV, certain species are capable of sustained intraspecies maintenance of particular viral variants adapted to those species. Such reservoir species are found among members of the order Carnivora (in the families Canidae, Herpestidae, Procyonidae, and Mephitidae), and Chiroptera (bats - only in the Americas). Molecular epidemiology studies of RABV isolates reveal several distinct lineages, the most widely distributed of which is the cosmopolitan lineage, thought to have originated in Europe and spread to many parts of the world with the movement of dogs during colonial times. Within this lineage, strains may cluster by geographic region into particular clades, such as the Africa 1a (northern Africa) and Africa 1b (southern Africa) clades. Distinct clades are also represented by virus strains (so-called ‘biotypes’) circulating in particular host species. These are the result of genetic adaptation of RABV variants to those species. Hosts of a particular virus biotype tend to be more susceptible to lethal infection with that biotype, and tend to excrete virus of the adapted biotype more readily than other biotypes. This leads to improved maintenance of the virus biotype in populations of that host species (hence the designation as ‘reservoir hosts’); however, it must be noted that spillover of host-adapted strains to other species occurs frequently, with occasional adaptation to those species. Rabies infection with any strain of RABV is fatal in all species, with little evidence of a carrier state where virus is shed in the absence of clinical progression of the disease.

Two biotypes of RABV occur in southern Africa, adapted to hosts belonging to the Canidae family (the canid biotype) and hosts belonging to the Herpestidae family (the mongoose biotype). In South Africa, the mongoose variant occurs principally in the yellow mongoose, although a number of early cases in genets (of the Viverridae family) gave rise to the misnomer ‘viverrid rabies’. Yellow mongooses, and mongoose rabies, are distributed over the central plateau of southern Africa. The major host species of the canid biotype in South Africa are dogs, black-backed jackals (*Canis mesomelas*) and bat-eared foxes (*Otocyon megalotis*). Rabies in jackals is predominantly seen in Limpopo Province and the adjacent North-West Province in the north, while rabies in bat-eared foxes has a geographic focus in the more arid western parts of the country (Northern and Western Cape Provinces).

Spillover infections into non-carnivorous mammals generally do not result in onward transmission of the virus from these dead-end hosts. A notable exception is rabies in greater kudus (*Tragelaphus strepsiceros*) in Namibia. Two extended epidemics have occurred, from 1975 through 1985 (during which an estimated 30,000 – 50,000 kudu died), and 2002 through 2012 (causing reductions of 30 – 70% in kudu populations). Epidemiological and phylogenetic evidence suggests that kudu populations are capable of maintaining the virus for extended periods (perhaps even indefinitely) following initial spillover of a canid variant, and that the virus is undergoing adaptation to its new host. Kudus are highly susceptible to infection by the oral route, and infected individuals excrete high concentrations of
rabies virus in saliva. Rabies virus is not ordinarily resistant enough for indirect transmission to occur through contamination of the environment with infected saliva, and it is believed that transmission between kudus was favoured by their propensity to indulge in self and mutual grooming, and by the fact that oral transmission is facilitated by the mouth injuries which kudus sustain when browsing on the *Acacia* thorn trees which predominate in the affected area. Individuals sometimes browse in close proximity to each other, particularly when population densities are high, so that transmission of infection through contamination of vegetation is a possibility.

Rabies is ordinarily transmitted by bite, and the occurrence and concentration of virus in saliva varies with virus biotype and host species. Virus is usually present in the saliva of infected animals at the time of onset of discernible illness. Its presence may be intermittent and may terminate one or two days before death. Virus has been demonstrated in saliva or salivary glands up to 13 days before the onset of illness in dogs. Factors which determine the successful transmission of rabies include the dose, route of administration and biotype of the virus, and the susceptibility of the recipient. The severity, location and multiplicity of bites inflicted on the victim also influence the outcome of exposure to infection, and bites on the head and neck are generally associated with the shortest incubation periods and the highest mortality rates. In the host, the virus gains entry into nerve endings through nicotinic acetylcholine receptors in neuromuscular junctions, or through sensory nerve endings of the epithelial/subepithelial tissues and mucous membranes. Once virus has entered nerves, there is passive centripetal transport of subviral genome-containing particles by retrograde axoplasmic flow to the central nervous system (CNS), followed by spread within the CNS. Although infection is usually widespread in the brain in the agonal stages of the disease, there is a tendency for lesions to be most advanced and for highest concentrations of virus antigen to occur in particular locations; these localizations may account for characteristic signs of the disease. Thus, early selectivity for the limbic system which controls the emotions, with relative sparing of the neocortex, could explain the initial retention of alertness with manifestation of aggressiveness and loss of fear which often characterizes the disease. From the time that the infection reaches the central nervous system, passive centrifugal spread of virus by anterograde axoplasmal flow proceeds simultaneously with centripetal spread. Spread to the salivary glands coincides with widespread dissemination of infection in the brain.

Rabies can occasionally be transmitted through non-bite exposure. Contact of infected saliva with mucous membranes or broken skin of a susceptible host, through for example licking, can transmit the infection. Oral infection through the ingestion of infected milk has been recorded, although consumption of pasteurized milk should not pose a danger. While there are reports of people developing rabies after skinning and butchering the carcasses of infected animals, it has never been recorded that humans have acquired the infection by ingesting the tissues of infected livestock. Aerosol transmission has been documented only in very unusual circumstances, including in two people who had separately visited a cave in the USA, home to a population of more than 20 million bats in which rabies virus infection was endemic. Infection has also been iatrogenically transmitted through organ transplantation from infected donors to recipients.

While unusual modes of transmission may be of interest in particular circumstances, it must be borne in mind that the vast majority of human exposures and deaths (> 90% worldwide) due to RABV infection result from contact with rabid dogs. Domestic dogs are the major reservoir in Africa and Asia,
and effective control of the disease in dogs is a necessary component of rabies control plans in these regions.