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Rabies and African bat lyssavirus encephalitis and its prevention

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ABSTRACT

Unlike any other human infection, encephalitis caused by dog rabies virus is always fatal. Rabies and other lyssaviruses have been found in unexpected places, and human disease, especially paralytic rabies, has gone unrecognised. Evidence is emerging that rabies-related bat lyssaviruses are enzootic across Europe, Africa, Asia and Australia, but none has been detected in the Americas. The epidemiology and origins of African lyssaviruses are discussed. Ideal rabies prophylaxis (pre-exposure immunisation followed by post-exposure booster vaccination) has proved 100% effective; hence all human deaths result from failure of prevention. Rabies vaccines of known quality are unaffordable for the majority in Africa. Although intradermal regimens requiring <40% of the usual vaccine dose are economical and are recommended by the World Health Organization, several problems have inhibited their use. A new, simplified, economical post-exposure vaccine regimen that uses an initial dose of intradermal injections at four sites overcomes many of the difficulties of the previous methods: it is at least as immunogenic as the standard intramuscular course of tissue-culture vaccine; is safer in inexperienced hands; requires fewer than two ampoules of vaccine and only three instead of five clinic visits. Recent data should increase the confidence of physicians to use the World Health Organization-accredited rabies vaccines more efficiently and at lower cost.

1. Incidence and epidemiology of human rabies

The true incidence of human rabies throughout the world is unknown. Official figures are underestimates because this is not a notifiable infection in many countries and patients do not always die in hospitals. For example, human rabies occurs in Egypt, where it is a notifiable disease, but no cases are reported to the World Health Organization (WHO). An estimate of the annual rabies mortality in Asia and Africa is 55 270 (90% CI: 24 000–93 000). Among these 23 705 are in Africa, suggesting an underreporting rate of 160 fold [1].

Rabies is a widespread zoonosis of certain mammal species in all continents except Antarctica. Genotype 1, classical rabies, infects terrestrial mammalian reservoir species and, in the Americas, bats. In the rest of the world, bat rabies is caused by rabies-related lyssaviruses (see below). A few places, usually islands and peninsulas, are claimed to be rabies-free, but imported rabies is possible anywhere. The epizootiology is constantly changing and local advice should be sought for detailed information.

Domestic dogs (*Canis familiaris*) are the principal reservoir species overall, the cause of more than 99% of human deaths [2]. They are the dominant reservoir in Asia, Africa and a few areas of Latin America. Although a rabid dog may appear wild and furious, it more often shows paralysis, with drooling of saliva, but dogs do not have hydrophobia. Dogs may transmit the virus to other mammals, commonly cats (which may become vectors), or man. Some wild animals are reservoirs. This sylvatic rabies occurs within a single species in a separate ecological compartment. The genetic characteristics of a virus isolate indicate its geographical origin and host species.

1.1. Terrestrial mammal rabies in Africa

African dog rabies was introduced by trade from Europe or Eurasia into North and West Africa over a century ago. Other carnivores were infected and some became reservoir species [3]. In North Africa, rabies is mainly an urban disease in dogs but there is sylvatic rabies in foxes (*Vulpes* spp.) and jackals [4], probably golden jackals (*Canis aureus*), and 1.2% of lesser Egyptian gerbils (*Gerbillus gerbillus*) in the Egyptian desert were found to be rabid [5]. In East Africa, outbreaks of rabies occur in Ethiopian wolves (*Canis simensis*), and in African wild dogs (*Lycaon pictus*) in Tanzania and Kenya.

In sub-Saharan Africa, dog rabies spread south, infecting other mammals such as the herbivorous kudu antelope (*Tragelaphus strepsiceros*), killing up to 20% of the population in Namibia. Jackals, predominantly black-backed jackals (*Canis mesomelas*), have become established reservoir species in Namibia, Botswana, Zim-

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Table 1
The Lyssavirus genus.

Genotype	Reservoir species [potential vectors][a]	Known distribution
Phylogroup I		
1 – Rabies virus	Dog, fox, raccoon, skunk, bats etc.	Widespread; bats in Americas only
4 – Duvenhage	Insectivorous bat (*Nycteris thebaica*)	South Africa, Zimbabwe, Kenya[b]
5 – European bat lyssavirus		
Type 1a	Insectivorous bats [sheep, cats]	Northern and Eastern Europe
Type 1b	Insectivorous bats	Western Europe
6 – European bat lyssavirus		
Type 2a	*Myotis dasycneme* bats	Netherlands, Germany
	Myotis daubentonii bats	UK
Type 2b	*Myotis daubentonii* bat	Switzerland, Finland
7 – Australian bat lyssavirus	Flying foxes (fruit bats)	Australia
	Insectivorous bats	
Phylogroup II		
3 – Mokola	Shrews, rodents [cats, dogs]	South Africa, Nigeria, Cameroon, Ethiopia etc[b]
2 – Lagos bat virus	Bats [cats, dog, water mongoose]	Zimbabwe, South Africa, Kenya[b]
	Has NOT been detected in man	

[a] Mammals infected by reservoir species may become vectors.
[b] See Fig. 1.

babwe and northern South Africa, as have bat-eared foxes (*Otocyon megalotis*) in South Africa [3].

Canine rabies spread south, reaching South Africa after World War II. However, recent evidence indicates that mongoose rabies is genetically distinct and was indigenous in the region a few hundred years before that. The infection is caused by different viral lineages found in several mongoose species (family: Herpestidae) including the yellow mongoose (*Cynictis penicillata*) and the slender mongoose (*Galerella sanguinea*).

A rise in human rabies mortality has often followed an increased incidence of canine infection, especially associated with wars or the movement of refugees. The AIDS epidemic has indirectly increased the risk of rabies infection in Kwa-Zulu Natal by expanding the number of ownerless dogs, which form roving feral packs [3].

2. Rabies-related lyssaviruses

Rabies in these terrestrial mammals is the classical genotype 1 virus, but there are seven members of the Lyssavirus genus in the Rhabdoviridae family (Table 1) – rabies and six genotypes of rabies-related virus, including European bat lyssavirus (EBLV) (genotypes 5 and 6); Australian Bat lyssavirus (ABLV) (genotype 7); and African genotypes 2 (Lagos bat virus), 3 (Mokola) and 4 (Duvenhage). Two of the African viruses are serologically and genetically distant and so are classed in the separate phylogroup II, while the rest are phylogroup I. All the rabies-related viruses have caused fatal infection in man, except for genotype 2 (Lagos bat virus), and all are bat viruses except genotype 3 (Mokola).

2.1. African rabies-related lyssaviruses

The distribution of the three African rabies-related viruses is shown in Fig. 1. Genotype 2, Lagos bat virus (LBV), a phylogroup II virus, is not known to infect man. It was first identified in fruit bats in Lagos, Nigeria [6], then in South African bats and more recently in Kenya. LBV was isolated from an Egyptian fruit bat (*Rousettus aegyptiacus*) imported into France from an uncertain source, probably either Egypt or Togo [7]. Data on bat infections are scarce, but a search for rabies in 436 bats in Egypt, published in 1969, included an unknown number of fruit bats and nine species of insectivorous bat. Seller's stain failed to reveal any Negri bodies in brain smears; however, mouse inoculation of pooled bat-brain samples yielded at least six transmissible agents that were not neutralised by antibody to viruses of rabies genotype 1 [8]. The species of origin and other details of interest are lacking, but since genotype 1 does not cross-protect against LBV it is possible that the group had isolated LBV but were unable to identify it.

Genotype 3, Mokola virus, the other phylogroup II virus, is less pathogenic than rabies and is the only rabies-related virus not found in bats; it is present in shrews and other rodents, which may infect cats and dogs. Mokola has been isolated from rabies-vaccinated animals, which is to be expected because it does not cross-react serologically with rabies. Two human infections, which were not typical of clinical rabies, have been reported in children in Nigeria and there is uncertainty about the diagnosis (Mokola virus was being handled in the laboratory at the time) [7]. A vaccinated laboratory worker had a very mild clinical infection [9].

Genotype 4, Duvenhage virus, has occasionally been found in insectivorous and fruit bats in South Africa, and caused fatal rabies-like encephalitis in three patients [7,10].

3. Rabies is a hidden disease

There is increasing evidence that lyssavirus infections are under-recognised, and that the diagnosis is missed in bats and in man. There have been 14 reported human cases of rabies-related lyssavirus infection, including six with EBLV and two with ABLV. However, these infections may easily be missed since the illness is indistinguishable from rabies encephalitis, which is almost always diagnosed clinically in Africa and Asia. The immunofluorescent antibody test (FAT) usually used for rabies diagnosis might be weakly positive or even negative with rabies-related viruses. Only a few specialised laboratories are able to distinguish between the genotypes and so they are only recognized by chance.

An example of this occurred in an unvaccinated doctor on holiday in Kenya, who was scratched on the cheek by a bat in 2007. The wound was washed with soap and alcohol. No lyssavirus had been reported in East African bats and no rabies post-exposure prophylaxis was advised. Three weeks later, back in the Netherlands, she developed neurological symptoms: dizziness, nausea, malaise, fever, dysarthria, hyperaesthesia of cheeks, unsteady gait and diplopia. A neurological diagnosis of hysterical conversion syndrome was made and she was treated with tranquillisers. After 4 days a generalised convulsion, incontinence, aspiration and hypoxia occurred. Brain stem encephalomyelitis was revealed by an MRI scan. Rabies was diagnosed by polymerase chain reaction (PCR) on a nuchal skin biopsy, which was also faintly positive by FAT. A saliva sample became PCR-positive at a later date. Despite intensive care the patient died of this rabies-like encephalitis 6 weeks after the incident [10]. The infecting virus proved to be Duvenhage