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CHAPTER

6

Bat Rabies

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1 INTRODUCTION

The detection of lyssaviruses in bat species during the 20th century has highlighted the role this complex group of mammals plays as the principal reservoir for genetically diverse lyssaviruses. There are over 1,100 recognized species of bats classified within the order Chiroptera, although distinction between species is often technically challenging due to morphological similarities between different species. The determination of bat species has been aided by the development of genetic tools that enable differentiation between very closely related species alongside the more traditional morphological and ecological classification techniques. Such techniques serve to classify groups of mammals as accurately as possible. As a result, bat species continue to be reclassified.

Currently, the order Chiroptera is divided into 19 different families that are further classified into numerous subfamilies and genera

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(Table 6.1). Additional classification has subdivided this order into suborders Vespertilioniformes and Pteropodiformes. The Vespertilioniformes includes three superfamilies of bats: the Emballonuroidae (sheath-tailed bats of the Old and the New Worlds that are divided across two subfamilies); the Noctilionoidea (a large highly diverse subfamily with seven families—some of which include omnivorous bat species); and the Vespertilionidea (the largest superfamily of insectivorous bats that includes four distinct families). The Pteropodiformes includes the family Pterpodidae (the Old World fruit bats sometimes referred to as the 'megabats') and five Old World families of insectivorous or carnivorous bats that make up the superfamily Rhinolophoidea, namely: the Craseonycteridae, the Hipposideridae, the Megadermatidae, the Rhinolophidae and the Rhinopomatidae (Hutcheon & Kirsch, 2006; Teeling et al., 2005). Across these suborders, bats can be described according to their feeding habits, and it is this feature of the bat life cycle that we will use to group lyssavirus infections of bats (Altringham, 2011; Giannini & Simmons, 2003) (Table 6.1). Detection of viral pathogens within different bat species, often highlighted through epizootics that have affected both human and animal populations, have fuelled extensive research into bats as hosts of viral pathogens. More recently, the detection of coronaviruses (Shirato et al., 2012), filoviruses (Towner et al., 2009) and henipaviruses (Halpin et al., 2011) have sparked further interest in bats as reservoirs of viral pathogens. However, it is the historical association of rabies virus and related lyssaviruses with bats that establishes this virus genus as the most notable zoonotic pathogen of bat origin.

Within bats, lyssaviruses have been characterized in only a small proportion of recognized species (Table 6.1). However, since the first descriptions of rabies virus in bats (Pawan, 1936), other divergent lyssavirus species have been detected in a wide range of chiropteran hosts. There are currently 12 defined lyssavirus species and a further 2 recently described viruses that all appear to cause, where reported, rabies pathogenesis in humans and terrestrial carnivores (Figure 6.1) (Kuzmin et al., 2010). Importantly, from the perspective of human vaccination, the different lyssavirus species have been divided into three phylogroups according to antigenic divergence and effectiveness of rabies vaccines. Phylogroup I viruses are all effectively neutralized by the current rabies vaccines, based on classical rabies virus strains while viruses categorized in phylogroups II and III are not neutralized by antibodies produced following standard rabies virus vaccination (Figure 6.1). Viruses include: *rabies virus* (RABV), which has been shown to infect a diverse range of species including bats in the New World and carnivores around the globe; *Lagos bat virus* (LBV), which has been detected in frugivorous bats, cats, and dogs but has not been associated with human

TABLE 6.1 The Current Classification of Bat Species and Association with Lyssavirus Infection

Suborder	Superfamily	Family	Genus Associated with Lyssavirus Infection	Lyssavirus Involved	Representative Reference
Pteropodiformes	Pteropodidae (Old world fruit bats)		Cynopterus	unidentified	Smith et al., 1967
			Eidolon	LBV	Kuzmin et al., 2008a
				MOKV	Kemp et al., 1972
			Eonycteris	unidentified	Lumlertdacha et al., 2005
			Epomophorus	LBV	Calisher et al., 2006; Crick et al., 1982
			Epomops	LBV	Calisher et al., 2006; Johnson et al., 2010
			Micropteropus	LBV	Calisher et al., 2006
			Pteropus	ABLV	Wong et al. 2007; Gould et al., 2002
				ARAV	Lumlertdacha et al., 2005
				IRKV	Lumlertdacha et al., 2005
				KHUV	Lumlertdacha et al., 2005
			Rousettus	EBLV-1	Calisher et al., 2006
				LBV	Markotter et al., 2008
				ABLV	Arguin et al., 2002
	Rhinolophoidea	Hipposideridae (Old World leaf-nosed bats	Hipposideros	SHIBV	Kuzmin et al., 2011a
		Rhinolophidae (Horseshoe bats)	Rhinolophus	EBLV-1	Calisher et al., 2006; Kuzmin and Rupprecht, 1999
				RABV	Jiang et al., 2010

(*Continued*)

TABLE 6.1 (Continued)

Suborder	Superfamily	Family	Genus Associated with Lyssavirus Infection	Lyssavirus Involved	Representative Reference
Vespertilioniformes	Emballonuroidae	Nycteridae (Slit-faced bats)	Nycteris	LBV	Calisher et al., 2006
				DUVV	Wong et al., 2007
		Emballonuridae (Sheath-tailed bats)	Saccolaimus	ABLV	Calisher et al., 2006; Wong et al., 2007
			Taphozous	ABLV	Arguin et al., 2002
	Noctilionoidea	Phyllostomidae (Leaf-nosed bats)	Anoura	RABV	Sodre et al., 2010
			Artibeus	RABV	Kobayashi et al., 2006; Price and Everard, 1977
			Carollia	RABV	Sodre et al., 2010
			Chrotopterus	RABV	Sodre et al., 2010
			Desmodus	RABV	Favoretto et al., 2002; Lopez et al., 1992
			Diaemus	RABV	Sodre et al., 2010
			Diphylla	RABV	Castilho et al., 2010
			Glossophaga	RABV	Salas-Rojas et al., 2004
			Leptonycteris	RABV	Constantine, 1979
			Lonchorhina	RABV	Sodre et al., 2010
			Lophostoma	RABV	Sodre et al., 2010
			Macrotus	RABV	Constantine, 1979
			Micronycteris	RABV	Salas-Rojas et al., 2004

	Mormoopidae (Ghost-faced bats)	Mormoops	RABV	Constantine, 1979
		Pteronotus	RABV	Salas-Rojas et al., 2004
	Phyllostomidae (Leaf-nosed bats)	Phyllostomus	RABV	Sodre et al., 2010
		Platyrrhinus	RABV	Sodre et al., 2010
		Sturnira	RABV	de Alemeida et al., 2011
		Trachops	RABV	Sodre et al., 2010
		Uroderma	RABV	Klug et al., 2011; Nunes et al., 2008
Vespertilionidea	Molossidae (Free-tailed bats)	Cynomops	RABV	Sodre et al., 2010
		Eumops	RABV	Constantine, 1979
		Molossops	RABV	de Rosa et al., 2011
		Molossus	RABV	Scheffer et al., 2007
		Nyctinomops	RABV	Constantine, 1979
		Tadarida	RABV	Constantine, 1979
		Tadarida	EBLV-1	Muller et al., 2007
	Miniopteridae (Bent-winged bats)	Miniopterus	ABLV	Arguin et al., 2002
			DUVV	Wong et al., 2007; Markotter et al., 2008
			EBLV-1	Calisher et al., 2006; Kuzmin and Rupprecht, 1999
			WCBV	Calisher et al., 2006

(*Continued*)

TABLE 6.1 (Continued)

Suborder	Superfamily	Family	Genus Associated with Lyssavirus Infection	Lyssavirus Involved	Representative Reference
		Vespertilionidae (Vesper bats)	Antrozous	RABV	Streicker et al., 2010; Burns et al., 1956
			Barbastella	EBLV-1	Muller et al., 2007
			Corynorhinus	RABV	Streicker et al., 2010; Constantine, 1979
			Eptesicus	RABV	Streicker et al., 2010
				EBLV-1	Calisher et al., 2006
			Euderma	RABV	Constantine, 1979
			Histiotus	RABV	Velasco-Villa et al., 2006
			Lasionycteris	RABV	Streicker et al., 2010
			Lasiurus	RABV	Streicker et al., 2010; Constantine, 1979
			Murina	IRKV	Calisher et al., 2006
			Myotis	ARAV	Arai et al., 2003; Gonzalez et al., 2008
				RABV	Streicker et al., 2010
				EBLV-2	Johnson et al., 2003
				EBLV-1	Muller et al., 2007
				KHUV	Kuzmin et al., 2003
			Nyctalus	EBLV-1	Muller et al., 2007
				RABV	Selimov et al., 1991
			Nycticeius	RABV	Constantine, 1979
			Philetor	ABLV	Arguin et al., 2002

	Pipistrellus	RABV	Constantine, 1979
		EBLV-1	Muller et al., 2007; Kuzmin and Botvinkin, 1996
		RABV	Constantine, 1979
	Plecotus	EBLV-1	Muller et al., 2004; Bouhry et al., 1992
	Scotophilus	ABLV	Arguin et al., 2002
	Vespertilio	EBLV-1	Kuzmin et al., 1994; Gonzalez et al., 2008
	Vespertilio	RABV	Selimov et al., 1991

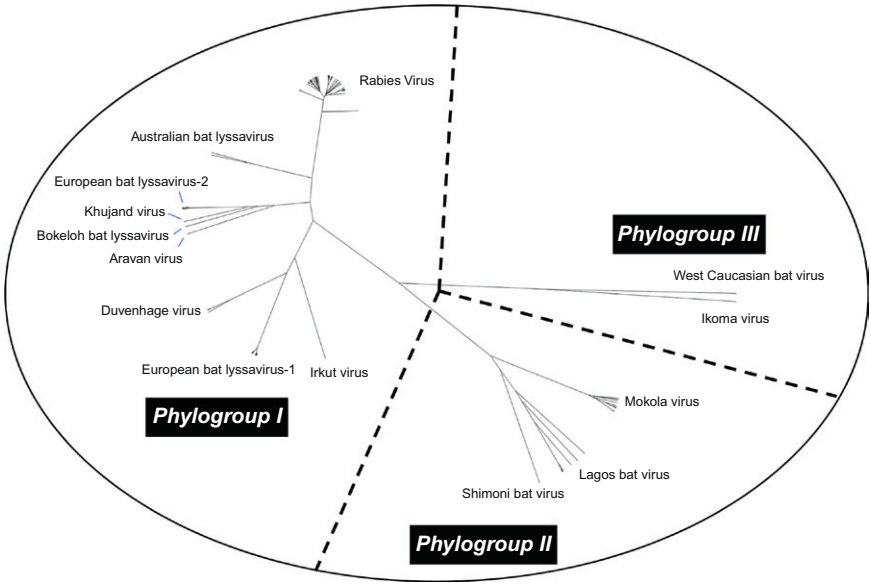

FIGURE 6.1 **Phylogenetic distance between lyssavirus species based on substitutions per site.** One hundred and ten lyssavirus nucleoprotein or full genomes sequences were analyzed in a Bayesian framework (BEAST v1.6.1). Posterior clade probabilities of all major nodes between lyssavirus species was >0.99.

infection (Kuzmin et al., 2008a; Markotter et al., 2006); *Mokola virus* (MOKV), which has caused natural infection of shrews, rats, cats, dogs, and two human cases (Sabeta et al., 2007); *Duvenhage virus* (DUVV), which has been isolated from insectivorous bats and has caused human fatalities following exposure to bat bites (Weyer et al., 2011); *European bat lyssavirus*-1 (EBLV-1), which has been detected primarily in insectivorous bats but has also been associated with cross species transmission (CST) events into what are considered dead-end hosts, including sheep, a stone marten, cats, and humans (Müller et al., 2007); *European bat lyssavirus*-2 (EBLV-2), which has been isolated from insectivorous bats alongside two documented human fatalities (Fooks et al., 2003a, b); *Australian bat lyssavirus* (ABLV) is endemic in frugivorous and insectivorous bats across Australasia and has also 'spilled over' into human populations (Moore et al., 2010); and *Irkut virus* (IRKV) that has caused human infection, *Aravan virus* (ARAV), *Khujand virus* (KHUV) and *West Caucasian bat virus* (WCBV) (Arai et al., 2003; Kuzmin et al., 2003, 2005, 2008b) that are all associated with insectivorous bats, although only single isolates exist for each species (Anonymous, 2009). Finally, in 2009, a virus isolated from a bat in Kenya and named *Shimoni bat lyssavirus* (SHIBV) (Kuzmin et al., 2010, 2011a) was classified by the ICTV

into the lyssavirus genus. Alongside these isolates, two currently unclassified lyssaviruses have also been identified that share high levels of genetic and morphological traits with the other lyssaviruses and are considered to be lyssaviruses. These have been reported in both volant and non-volant species and include the following. In 2010, a novel lyssavirus was detected in a Natterer's bat (*Myotis nattererii*) in Germany and was named *Bokeloh bat lyssavirus* (BBLV) (Freuling et al., 2011); and in 2011 a novel lyssavirus was detected in an African civet (*Civettictis civetta*) in Tanzania and was subsequently named *Ikoma Lyssavirus* (IKOV) from the location where the civet was captured (Marston et al., 2012). Each of these isolates has yet to be classified within the lyssavirus genus but ultimately represents new lyssavirus species. Where novel lyssaviruses have been associated with bat infections, they are detailed further in sections that follow.

Along with the ecological evidence that Chiroptera are the original reservoirs of lyssaviruses, there is strong phylogenetic support for this with evidence of bat-derived viruses having evolved long before those RABV of terrestrial carnivore origin (Badrane & Tordo, 2001). Despite this, there remain two distinct lyssaviruses that have not yet been detected in bat species: MOKV and IKOV. In the case of MOKV, the reservoir remains unclear. Numerous virus isolates have been reported from different species, including organ pools from shrews (*Crocidura* sp) in Nigeria (1968) (Kemp et al., 1972; Shope et al., 1970) and Cameroon (1974) (Le-Gonidec, Rickenbach, Robin, & Heme, 1978) (Swanepoel, 1994); domestic cats (*Felis catus*) in South Africa (1970, 1995–1998), Zimbabwe (1981–1982) (Foggin, 1983) and Ethiopia (1989–1990) (Mebatsion, Cox, & Frost, 1992); and the rusty-bellied brush furred rat (*Lophuromys sikapusi*) in the Central African Republic (1983) (Saluzzo et al., 1984). Although human infection has been reported, a fatal (Sabeta et al., 2007) outcome of infection was only recorded in one instance, and so the threat to the human population remains hard to determine (Familusi et al., 1972; Sabeta et al., 2007). Infections with MOKV are rare, with scant surveillance initiatives and limited diagnostic capacity, perhaps perpetuating our lack of knowledge of this lyssavirus (Sabeta et al., 2007). Although MOKV antibodies have been detected in bat species, it is widely accepted that this is due to cross reactivity with antibodies against LBV, rather than evidence of MOKV circulation, although further sampling of different bat species may discover that MOKV also circulates in bats in the Old World (Dzikwi et al., 2010; Kuzmin et al., 2008a). The phylogenetic relationship and current thoughts regarding host susceptibility of MOKV have been reviewed by Markotter and co-workers (2008).

In contrast to MOKV, where multiple isolates have been characterized and CST events have been identified, for IKOV, only a single isolate exists. The discovery of IKOV was the first detection of a non-rabies lyssavirus in

African civets. Furthermore, the detection of this virus within the boundaries of the Serengeti National Park, Tanzania, during routine dog rabies surveillance activities highlights the importance of molecular characterization of virus isolates where surveillance initiatives are in place (Marston et al., 2012; Mebatsion, Cox, & Frost, 1992). Analysis of sequence data generated from infected samples indicates that IKOV is the most divergent lyssavirus reported (Figure 6.1). The Serengeti National Park has been free of classical dog rabies for many years, with rabies cases clustering outside of the park in neighboring villages. Therefore, the isolated detection of this lyssavirus within the park from a terrestrial and largely solitary species strongly suggests that IKOV represents a CST event that could be of bat origin given the viruses close phylogenetic relationship with WCBV (Marston et al., 2012).Without further isolates of this and more closely related lyssaviruses the reservoir for IKOV remains to be elucidated.

The evolutionary history of lyssaviruses within bats remains unresolved. Across the New World, only variants of classical RABV are associated with the infection of bat species, whereas other lyssaviruses remain completely absent across the New World in either volant or nonvolant mammalian populations. Indeed, RABV has been detected in more than 50 species of insectivorous bat across the New World alone (see Section 6.2). In direct contrast, across the Old World there have been no detections of classical RABV strains in any bat species despite the presence of classical RABV in terrestrial species. Instead, 12 genetically divergent non-RABV lyssaviruses have been characterized from different bat species in the Old World. The reason for this situation remains unclear, however, tests for neutrality using various evolutionary algorithms on a panel of lyssavirus G protein sequences suggest neutral evolution occurs for lyssaviruses, and therefore niche-partitioning and radiation may explain this genetic pattern (Badrane & Tordo, 2001). Interestingly, where different bat species have been associated with lyssavirus infection, there often appears to be, to some extent, a host restriction to infection with genetically distinct lyssaviruses. RABV itself may be exploiting relatively new niches in previously uninfected New World bats (Streicker et al., 2010). The focus of this chapter will be the association of different lyssavirus species with bats across the globe. Lyssavirus species will be described according to the bat species most frequently associated with infection and to avoid repetition, different species will be described according to their feeding patterns.

2 LYSSAVIRUSES AND INSECTIVOROUS BATS

In this section, we will discuss the association of classical RABV with numerous insectivorous bat species across the New World and comment

on recent findings regarding the occurrence of CST events. We will then detail the occurrence of lyssaviruses in insectivorous bats in the Old World, concentrating on what appear to be principal reservoirs of each of the genetically distinct lyssaviruses.

2.1 Rabies Virus in Insectivorous Bats of the New World

2.1.1 Historical perspectives

Prior to the 1950s, insectivorous bats were not considered a source of rabies in the New World. This changed in 1951 with the first documented case of human rabies resulting from a bat bite (Enright et al., 1955). Human infection with insectivorous bat-derived RABV was again reported in the United States in 1954. In the summer of 1953, a seven-year-old boy was attacked and bitten by a rabid Florida yellow bat (*Lasiurus intermedius*) (Venters et al., 1954). Subsequent surveillance for RABV in bats detected 40 cases between 1953 and 1958 (Scatterday, 1954) and the direct transmission of RABV following the bite of a naturally infected insectivorous bat was shown experimentally through transmission to suckling mice (Bell, 1959). This unequivocally highlighted the public health threat of rabid insectivorous bats and brought a new aspect of RABV epidemiology to the interest of the scientific community. Since these early reports of rabies in insectivorous bat populations, surveillance throughout the United States has detected rabies within indigenous insectivorous bat species from almost every state (Mondul, Krebs, & Childs, 2003). The first rabid bats in Canada were reported in 1957 (Avery & Tailyour, 1960). Infected species included the big brown bat (*Eptesicus fuscus*), the little brown bat (*Myotis lucifugus*), and the silver-haired bat (*Lasionycteris noctivagans*), all reported from British Colombia. Detection of RABV infected insectivorous bats has been reported in Mexico since 1953 and South America since the 1960s (Baer & Smith, 1991).

2.1.2 Natural and Experimental Infection of Insectivorous Bats

Insectivorous bats infected with RABV show a variety of disease signs that parallel infection in other mammals. A number of studies have described the susceptibility to infection and the clinical signs of disease in different insectivorous bat species. An early study by Baer and Bales (1967) with the Mexican free-tailed bat (*Tadarida braziliensis*) confirmed the susceptibility to infection with a RABV isolated from the same species. Inoculation by the intracranial, intramuscular, and subcutaneous routes caused clinical disease in bats over a range of virus titers. Infected bats displayed signs of aggression, weakness, and anorexia with relatively short morbidity periods ranging from 4 to 20 days. Importantly, the intermittent excretion of virus in saliva was observed during this period, a feature of virus transmission that remains poorly understood.

No evidence of virus excretion in the absence of disease development was observed. A recent infection study reported RABV infection of the big brown bat (*Eptesicus fuscus*), again using virus derived from the salivary glands of the same species (Jackson et al., 2008). In this study, bats infected intramuscularly exhibited weight loss, ataxia, and paresis. Transmission by bite is considered the most common method of RABV transmission in bats although there is evidence that aerosolized virus may cause infection in roosts where large numbers of bats congregate, such as the Mexican free-tailed bat (Baer & Smith, 1991). Interestingly, experimental studies of North American RABV variants did not demonstrate evidence of disease in bats but showed seroconversion against RABV in response to exposure to aerosolized virus (Davis, Rudd, & Bowen, 2007). This may account for the levels of seropositivity observed in many bat populations around the world.

The striking feature of the ecology of lyssaviruses in the New World in comparison to that of the Old World is the diversity of bat species that appear to act as a virus reservoir. Prior to the introduction of molecular differentiation techniques it was impossible to differentiate between RABV isolates. The application of panels of monoclonal antibodies that targeted the virus nucleoprotein revealed antigenic differences between RABV and other members of the lyssavirus genus (Wiktor & Koprowski, 1980). This approach demonstrated that RABV variants from North America could be differentiated and that different virus isolates were often associated with the reservoir host, including a range of non-flying species such as the red fox (*Vulpes vulpes*), racoons (*Procyon lotor*), and skunks (*Mephitis mephitis*) (Smith, 1988). RABV from particular bat species also showed distinctive monoclonal antibody binding patterns. This was confirmed in both Canada (Nadin-Davis et al., 2001) and Mexico (Velasco-Villa et al., 2002). Importantly, it was also noted that the only lyssavirus species isolated in New World bats, and indeed all non-bat reservoirs, are variants of RABV, with no detection of non-RABV lyssaviruses being reported in the Americas. This has been confirmed by the application of phylogenetic techniques based on the RABV genome, which show that particular bat species are associated with specific RABV variants (Hughes, Orciari, & Rupprecht, 2005; Streicker et al., 2010; Velasco-Villa et al., 2006). This is described further in later sections.

Numerous studies from individual states within the United States (Burnett, 1989; Childs, Trimarchi, & Krebs, 1994; Crawford-Miksza, Wadford, & Schnurr, 1999) and Canada (Nadin-Davis et al., 2001) have reported multiple insectivorous bat species to be rabid, although it remains unclear what properties of bats make them a successful host for rabies virus. Table 6.2 compares the number of rabid bats reported in the United States between 1993 and 2000 (Mondul, Krebs, & Childs, 2003),

TABLE 6.2 A Comparison of Bat Species Testing Positive for Rabies Virus from Two Reports from within the United States

		1993–2000[a]	2010[b]
Species	**Common Name**	**No. (% of species tested)**	
Antozous pallidus	Desert pallid bat	21 (21.0)	2 (6.9)
Eptesicus fuscus	Big brown bat	1,216 (5.8)	324 (3.8)
Euderma maculatum	Spotted bat	1 (100)	NR
Lasionycteris noctivagans	Silver-haired bat	73 (12.9)	14 (6.7)
Lasiurus borealis	Red bat	47 (9.0)	40 (23.5)
Lasiurus cinereus	Hoary bat	97 (38.2)	16 (33.3)
Lasiurus ega	Southern yellow bat	7 (21.9)	2 (33.3)
Lasiurus intermedius	Northern yellow bat	3 (100)	16 (18.8)
Lasiurus seminolus	Seminole bat	0 (0.0)	6 (30.0)
Lasiurus xanthinus	Western yellow bat	NR	3 (100.0)
Myotis californicus	California myotis	12 (3.6)	0 (0.0)
Myotis evotis	Long-eared myotis	19 (9.7)	6 (14.6)
Myotis keenii	Keen's myotis	11 (1.9)	NR
Myotis lucifugus	Little brown bat	96 (1.7)	26 (2.9)
Myotis thysanodes	Fringed myotis	0 (0.0)	1 (50.0)
Myotis volans	Long-legged myotis	3 (13.0)	1 (16.7)
Myotis yumanensis	Yuma myotis	4 (1.7)	1 (5.9)
Myotis (unspeciated)	Unspeciated myotis	41 (6.1)	8 (8.4)
Nycticeius humeralis	Evening bat	6 (9.7)	5 (4.8)
Nyctinimops (Tadarida) femorosaccus	Pocketed free-tailed bat	7 (13.2)	NR
Tadarida macrotis	Big free-tailed bat	3 (21.4)	4 (57.1)
Parastrellus Hesperus	Canyon bat	NR	14 (21.5)
Myotis austroriparius	Southeastern myotis	NR	1 (11.1)
Perimyotis subflavus	Tri-colored bat	NR	5 (25.0)
Pipistrellus Hesperus	Western pipistrelle	41 (21.2)	NR
Pipistrellus subflavus	Eastern pipistrelle	20 (17.1)	NR
Plecotus townsendii	Townsend's big-eared bat	3 (10.3)	0 (0.0)

(*Continued*)

TABLE 6.2 (Continued)

Species	Common Name	1993–2000[a] No. (% of species tested)	2010[b] No. (% of species tested)
Tadarida brasiliensis	Brazilian/Mexican free-tailed bat	214 (31.8)	286 (65.4)
Tadarida unspeciated	Unspeciated free-tailed bats	1 (33.3)	NR
Unspeciated	Unspeciated bats	NR	648 (4.9)

NR Not Reported.
[a]Data obtained from Mondul et al. (2003). A total of 31,380 bats were tested with 1,946 (6.2%) testing positive for rabies virus. Bat species that were negative have been removed from the table.
[b]Data obtained from Blanton et al. (2011). A total of 24,298 bats were tested with 1,430 (5.9%) testing positive for rabies virus.

with the numbers reported during 2010 (Blanton et al., 2011). A number of species are consistently reported with high levels of rabid submissions in both surveys, including the big brown bat (*Eptesicus fuscus*), the silver-haired bat (*Lasionycteris noctivagans*), the red bat (*Lasiurus borealis*), the hoary bat (*Lasiurus cinereus*), the little brown bat (*Myotis lucifugus*), and the Mexican free-tailed bat (*Tadarida braziliensis*). A comparison of four species of North American insectivorous bats that are most commonly reported as rabid (Table 6.3) indicates that traits such as colony size or geographical distribution do not support any particular hypothesis for their association with RABV. Indeed, it appears that the majority of North American bat species have been associated with RABV infection to varying extents. Recent phylogenetic analysis of RABV species isolated from North American bat species suggests that a model of CST followed by virus evolution within a particular host species fits the current diversity of the virus within insectivorous bats (Streicker et al., 2010). This implies that the majority of RABV transmissions within bats are intra-species events. It also suggests that the transmission of bat variants of RABV from a bat to other mammals, including humans, is a rare event. Experiments from the 1960s demonstrated that bat variants of RABV could infect a range of carnivores, although some species showed greater susceptibility than others (Constantine, 1966a,b). In addition to inoculation by intramuscular injection, transmission to conspecifics was also demonstrated by repeated biting, in some cases over one hundred times, by an infected Mexican free-tailed bat (Constantine, 1966c). Examples of bat variant infections in non-bat species have been reported, including from Canada where CST of a bat variant to a squirrel was reported (Webster, Casey, & Charlton, 1988) as well as that of

TABLE 6.3 Comparison of Four Insectivorous Bat Species Associated with Transmission of Rabies to Humans in North America

Characteristic	Tadarida Brasiliensis	Eptesicus Fuscus	Lasionycteris Noctivagens	Perimyotis Subflavus
Common name	Mexican/ Brazilian free-tail bat	Big brown bat	Silver-haired bat	Tri-colored bat
Distribution	Found throughout the Western hemisphere from northern United States to Eastern Brazil	Found throughout southern Canada and United States to northern South America	Found throughout Canada, United States, and northern Mexico	Found in the eastern regions of Canada and United States
Description	The species grows to about 9 cm in length and weighs around 12 g	The species grows to 12 cm in length and can weigh about 20 g	The species grows to about 10 cm in length, and adults can weigh between 8 and 12 g	The species grows to 9 cm in length, and adults weigh between 4 and 10 g
Colony size	Can reach up to 20 million in size	Maternity colonies have been measured in the hundreds (300–600)	Solitary species.	Generally solitary, although females form small maternity colonies (<20 individuals)
Roost in human structures	Yes	Yes	No	No

CST to two red foxes and a cow (Webster, Casey, & Charlton, 1989). Such CST events are rare, and in the majority of cases there has been no evidence of onward transmission and maintenance of the infecting virus isolate within the new host species. However, two very rare events where CSTs have led to the maintenance of virus in the non-chiropteran host have been documented. One such event occurred on Prince Edward Island, Canada, where a cluster of rabies cases in red foxes (*V. vulpes*) was observed. Screening of the viruses isolated, with a panel of 15 monoclonal antibodies, suggested that they were of bat origin, possibly the little brown bat (*Myotis lucifugus*) (Daoust, Wandeler, & Casey, 1996). A larger epizootic occurred following the emergence of rabies in the skunk (*M. mephitis*) population in the state of Arizona (Leslie et al., 2006). Sequence analysis of the RABV genome recovered from 19 skunks demonstrated that the source of the infection was likely to be from a

RABV variant normally found in the big brown bat (*Eptesicus fuscus*). It is notable that CST events are more commonly reported with RABV than other lyssaviruses, possibly as RABV was more recently introduced into the New World bats. In contrast the bat-associated lyssaviruses in the Old World are considered to be evolutionarily older viruses (Tordo and Badrane, 2001; Noel Tordo, personal communication). These examples of sustained transmission among non-bat hosts are likely examples of how RABV emerged as a pathogen of carnivores, including domestic dogs.

2.1.3 Human Infection

Human infection with RABV of insectivorous bat origin is increasingly being recognized now that rabies has been eliminated from the domestic dog population in North America. At least 61 cases of human rabies between 1950 and 2007 were identified that could be attributed to transmission from bats (De Serres et al., 2008; Messenger, Smith, & Rupprecht, 2002). In one extreme case, transplant material from a human case of rabies of bat origin was transferred to four recipients who then developed the disease (Srinivasan et al., 2005). Table 6.4 shows the number of human cases in the United States between 2002 and 2010. From these data, it is apparent that the transmission to humans, although rare, occurs from a small group of species. Investigation of one of these variants isolated from the eastern pipistrelle bat (*Pipistrellus subflavus*) suggested that this virus possessed certain virological characteristics, such as increased replication in epithelial cells and growth at lower temperatures, which may enhance the ability of the virus to be transmitted by a bite (Kuzmin et al., 2012; Morimoto et al., 1996). Interestingly, one rare survivor of RABV infection was believed to have been infected with a bat-variant of the virus (Willoughby et al., 2005). Due to the recognition that rabies virus transmission from bats represents a high risk following contact, rabies post-exposure prophylaxis is recommended for any encounter with an insectivorous bat.

Until recently, the association of RABV with South American insectivorous bats has been neglected, mainly due to the burden of rabies cases associated with hematophagous species of bat. However, the report of a human rabies case transmitted from a Brazilian free-tailed bat (*Tadarida braziliensis*) (Favi et al., 2002) highlighted the role that insectivorous bats play in the ecology of RABV and the risks to public health. An additional study updated the list of all bat species (insectivorous, frugivorous, and hematophagus) that have been shown to be positive for RABV in Brazil and included 41 species from the families *Molossidae*, *Phyllostomidae*, and *Vespertilionidae* (Sodre, da Gama, & de Almeida, 2010). The wealth of sequence data available for RABV isolates from New World bat species has led to detailed attempts to create genealogical trees that include all bat reservoir species (Oliveira et al., 2010). This approach confirmed earlier findings on the association between particular virus lineages and

TABLE 6.4 Human Cases of Rabies in the United States of Bat Origin

Year	Total Human Rabies Cases	Cases Due to Bat Variants	Suspected Bat Reservoir
2002	3	3	*Tadarida brasiliensis*
			Perimyotis subflavus
			Lasionycteris noctivagens/ *Perimyotis subflavus*
2003	3	1	*Lasionycteris noctivagens*
2004	8	6	*Tadarida brasiliensis* (×5)[a]
			Unknown bat
2005	1	1	Unknown bat
2006	3	2	*Tadarida brasiliensis*
			Lasionycteris noctivagens
2007	1	1	Unknown bat
2008	2	2	*Tadarida brasiliensis* related
			Lasionycteris noctivagens
2009	4	3	Unknown bat
			Perimyotis subflavus
			Desmodus rotundus
2010	2	2	*Desmodus rotundus*
			Perimyotis subflavus

(Adapted from Blanton et al., 2011.)
[a]*related to transplantation in four cases.*

bat species separating RABV variants into at least 14 groups. A general observation was the influence of geographical separation of certain species that are located in both North and South America. For example, the RABV variants associated with *Tadarida braziliensis* formed two clusters dependent on the geographical origin of the bat. This was consistently shown for both *Myotis* and *Eptesicus* species. The surprising exceptions to this were those RABV viruses associated with *Lasiurus* species (*L. cinereus*, *L. borelialis* and *L. ega*), which formed a single group (Oliveira et al., 2010). The reasons for this close association between North and South American RABVs are uncertain. However, the hoary bat (*L. cinereus*) is known to make large distance migrations although this is limited to migration from the interior of the United States to over-wintering sites on the coastline and possibly central Mexico

(Cryan & Wolf, 2003). It is possible that there is sufficient overlap of migrating hoary bat populations between Canada and Brazil to have enabled the observed passage of RABV between both continents.

2.2 Rabies in Insectivorous Bats of the Old World

In direct contrast to the situation seen in the New World, where closely related RABV isolates are associated with numerous different insectivorous bat species, in the Old World highly divergent non-RABV isolates have been reported from very few bat species. Due to the paucity of knowledge about other lyssaviruses of the Old World associated with the infection of insectivorous bats, we concentrate on what is known about infection with the EBLVs.

2.2.1 Lyssavirus Infection of Serotine Bats

Serotine bats are considered to play a key role in the epidemiology of bat rabies in Europe. Indeed, the first link to a rabies-like infection was established in 1954 when the first report of a rabid bat in Europe was made in Germany (Mohr, 1957). The species of bat involved in this incident was not reported, although subsequent detections of lyssaviruses in serotine bats may suggest that early bat rabies cases in Europe involved this species. Only with the advent of antigenic typing and molecular tools could the virus isolated in European bats be distinguished from classical RABV and other lyssavirus species (Bourhy et al., 1992; Schneider & Cox, 1994). Serotine bats belong to the genus *Eptesicus* of the subfamily Vespertilioninae, chiropteran family Vespertilionidae of the suborder Vespertilioniformes. Up to 39 insectivorous species of *Eptesicus* are known to exist (Hutson, Mickleburgh, & Racey, 2001; Niethammer & Krapp, 2011). Of the 39 species of *Eptesicus*, *E. serotinus isabellinus* and *E. serotinus* deserve special attention, as they are primarily associated with transmission of EBLV-1. *E. serotinus* is the most widespread and abundant Palaearctic species of *Eptesicus* in Europe. Its present range extends from the Atlantic Ocean and the Mediterranean basin to Northern Denmark and the Eastern parts of the Eurasian continent as far as the Pacific seaboards, with evidence for an expansion into Scandinavia (Figure 6.2A) (Hutson et al., 2008). *E. s. isabellinus* has been reported in North Africa and Southern Iberia and is considered to be genetically divergent from *E. serotinus* (Ibanez, García-Mudarra, Ruedi, Stadelmann, & Juste, 2006).

2.2.1.1 EPIDEMIOLOGY OF LYSSAVIRUS INFECTION OF SEROTINE BATS

Serotine bats are one of the most studied lyssavirus reservoir species, revealing some fundamental insights into virus–host interactions and, hence, possibly the epidemiology of bat lyssavirus infections in

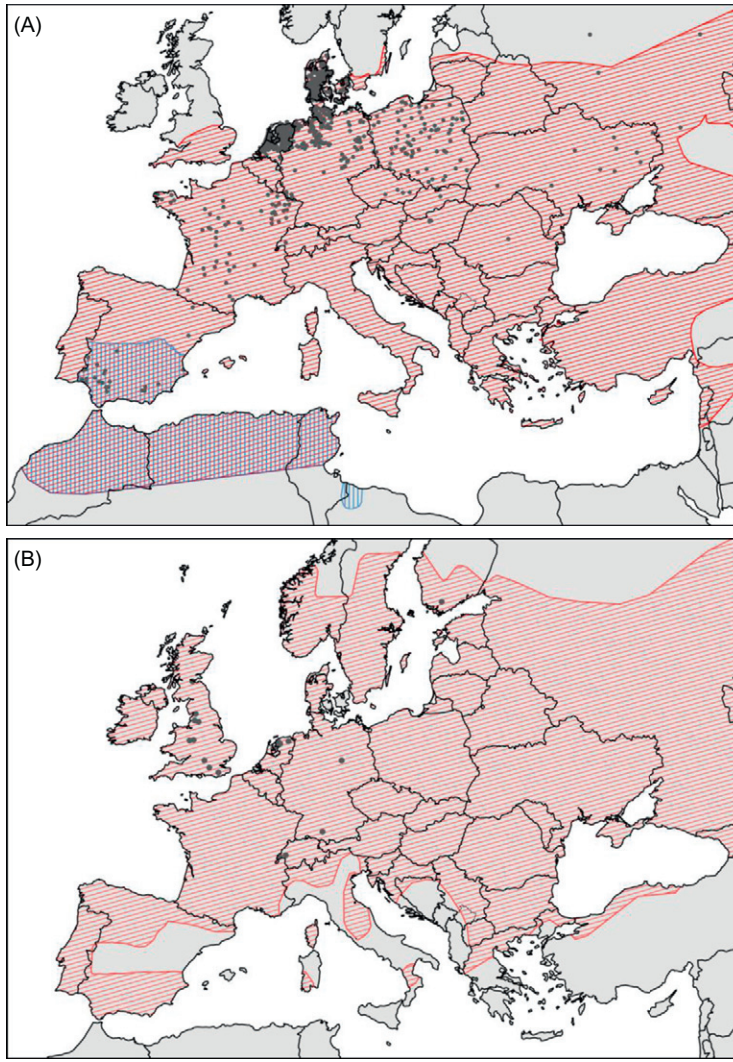

FIGURE 6.2 Distribution of the insectivorous bat species found to be infected with, and reported cases of, EBLV-1 and EBLV-2. A) Range of *E. serotinus* (Red) and *E. isabellinus* (Blue) and reported EBLV-1 cases (dots); B) Range of *M. daubentonii* (Red) and EBLV-2 (dots) cases in Europe 1977–2010. Distribution of bats according to IUCN and Vazquez-Moron, 2011.

insectivorous bat species in the Old World. *E. serotinus* and *E. s. isabellinus* are known to be associated with EBLV-1 and thus, are considered the primary reservoir hosts for this particular bat-associated lyssavirus. Interestingly, of the 959 cases of bat rabies officially reported between 1977 and 2010 to the database of the Rabies Bulletin Europe (RBE) about

95% have been observed in *E. serotinus* (Schatz et al., 2012). The involvement of *E. s. isabellinus* in the epidemiology of EBLV-1 was demonstrated in southern Spain when rabid serotine bats were later genetically identified as Isabelline serotine bats (Perez-Jorda et al., 1995; Vazquez-Moron et al., 2008a; Vazguez-Moron et al., 2008b). During the past 50 years, the vast majority of rabid serotine bats in Europe have been diagnosed in densely populated countries of The North European Plain that covers large areas of Denmark, The Netherlands, and Germany. However, this clustering of reported bat rabies cases suggests a bias in surveillance activities that reflects the location of established networks of bat handlers and their activities (Figure 6.2A). Regardless of this potential bias in sampling, it seems clear that the serotine bat has particular host species-specific ecological traits that may promote the maintenance and transmission of EBLV-1. Indeed *E. serotinus* is a very adaptable species with habitats including semi-desert, temperate, and subtropical dry forest, Mediterranean-type scrubland, farmland, and suburban areas. Furthermore, in contrast to other bat species, it is not experiencing a decline in population size. Hence, a greater abundance of *E. serotinus* might favor virus amplification and may explain the clusters of bat rabies cases detected in densely populated areas. The northern distribution range of serotine bats seems to be limited by a threshold level of mean summer temperatures (Harbusch, 2003). Interestingly, the great majority of EBLV-1–infected *E. serotinus* have been reported from this northern range. This is supported by surveillance for EBLV-1 in Germany, a country with a north-south gradient in elevation where over several decades notably higher numbers of cases have been reported from the northern regions of the country, where the highest density of *E. serotinus* is found (Müller et al., 2007). Taking this into account might explain why in some European countries with existing *E. serotinus* populations, no or only sporadic cases of EBLV-1 infections are observed (Anonymous, 2012; Van der Poel et al., 2005). Despite the limitations of surveillance, based on the current knowledge of EBLV-infections it is likely that serotine bats may be infected with EBLV-1 throughout Eurasia (Schatz et al., 2012). For reasons unknown, however, long-term active and passive surveillance for lyssaviruses has provided no evidence for EBLV-1 circulation in serotine bat populations in southern England, although specific antibodies have been detected in a single serotine bat (Harris et al., 2009). This disparity between mainland Europe and the UK may be due to the limited geographical distribution and population size of *E. serotinus* within the UK preventing EBLV-1 persistence.

The molecular characterization of EBLV-1 isolates from serotine bats has revealed valuable clues to virus–host interactions and help resolve questions surrounding the epidemiological puzzle of this virus–host

relationship. With approximately 5×10^5 substitutions per site per year the evolutionary rate of nucleotide substitution of EBLV-1 is one of the lowest recorded for RNA viruses, suggesting that the current genetic diversity of the virus in serotine bats arose between 500 and 750 years ago (Davis et al., 2005) although other estimates predict a more recent evolution (Hughes, 2008). Either way, this is believed to reflect an evolutionary stability between EBLV-1 and its two host species (Davis et al., 2005). Based on unique molecular traits, however, there is evidence that the phylogeny of this virus is more complex than previously thought and clearly associated with geographically different host evolutionary history (Vazquez-Moron et al., 2011). Early genomic sequencing indicated that in European populations of serotine bats two distinct genetic lineages of EBLV-1 evolved, which seemed to geographically cluster (Amengual et al., 1997). Serotine bats throughout the North and East European Plains, for example, located between the North Sea and the Baltic Sea to the north, and the Central European Highlands to the south, are infected by EBLV-1 lineage "a." These isolates have been reported to exhibit an extremely high sequence identity, as confirmed by phylogenetic analysis of the N-gene (Amengual et al., 1997; Davis et al., 2005; Freuling et al., 2008; Van der Poel et al., 2005). Despite its extensive West-East geographic range, the low genetic diversity in connection with a consistent star-like structure of the phylogenetic network suggests a relatively recent introduction, evolution, and rapid expansion of EBLV-1a variants in populations of serotine bats in these parts of Europe (Vazquez-Moron et al., 2011). Although in early studies no, or only a less pronounced, correlation between geographic and genetic distances was observed with lineage 1a using both a hypothetical introduction point or a model based origin of a putative common ancestor (Amengual et al., 1997; Davis et al., 2005), cluster analysis showed a significant positive correlation between genetic and temporal and spatial distance based on N-gene sequence and provided evidence for a geographical segregation (Freuling et al., 2008a, 2012a). EBLV-1a isolates from serotine bats within certain geographical regions of The Netherlands and Germany have almost identical nucleotide sequences. This indicates genomic stability during the transmission cycle of these virus variants, with little geographic spread or intermixing (Freuling et al., 2008a; Van der Poel et al., 2005). Serotine bat colonies usually number 10 to 50, although occasionally up to 300 individuals have been recorded (Hutson et al., 2008; Niethammer & Krapp, 2011). Considering the sedentary nature of the serotine bat (Hutson et al., 2008) transmission of EBLV-1a over long distances may not play a major role in EBLV-1 epidemiology (Freuling et al., 2008a; Van der Poel et al., 2005) and therefore somewhat contradicts a rapid expansion hypothesis of EBLV-1a variants in populations of serotine bats.

In contrast to EBLV-1a, EBLV-1 lineage 'b' appears to follow a more North-South distribution (Figure 6.2A) and is genetically more heterogeneous (Amengual et al., 1997). This heterogeneity is reflected by the presence of diverse sublineages that are predominantly associated with populations of serotine bats on the Iberian Peninsula, in The Netherlands, France, and southwestern Germany (Davis et al., 2005; Müller et al., 2007). A recent phylogenetic analysis segregated *E. s. isabellinus* sequences from the *E. serotinus* sequences and hypothesized that the *E. s. isabellinus* isolates form a further independent lineage, EBLV-1 lineage 'c' (Vazquez-Moron et al., 2011). Considering that serotine bats do not normally migrate over large distances, recent single discoveries of EBLV-1b in Central Poland and Eastern Germany (Müller et al., unpublished data; Smreczak et al., 2007) may suggest that the distribution of this lineage is more widespread in Europe than previously considered. As there is evidence of genetic flow between *E. s. isabellinus* populations on both sides of the Strait of Gibraltar, there is reason to believe that North African conspecifics may also be infected with this lineage (Juste et al., 2009).

It remains unclear, however, exactly how populations of serotine bats in different parts of Europe favor the current geographic distribution and clustering of the two or three different EBLV-1 lineages. Additional genetic data from both the host species and virus isolates are required to fully understand the evolutionary EBLV-1-serotine bat interaction. In any case, serotine bats in the westernmost parts of the North European Plains represent the only geographical location where both EBLV-1a and EBLV-1b are detected (Van der Poel et al., 2005; Picard-Meyer et al., 2006). However, as co-infection of serotine colonies or infection of individuals with both lineages has not been reported, this may suggest independent infectious cycles among *E. serotinus*. Interestingly, results of recapture data and long-term active rabies surveillance in maternity colonies of *E. s. isabellinus* strongly suggest close communities in which variants of EBLV-1 independently circulate (Vazquez-Moron et al., 2008b). Also, provided the hypothesis of an inverse correlation between CST of lyssaviruses and phylogenetic distance between bat species as recently demonstrated for North American bat RABV also applies to European bats (Streicker et al., 2010), then future targeted surveillance should discover the existence of known or new EBLV-1 lineages.

2.2.1.2 CLINICAL INFECTION AND DISEASE PATTERNS

Based on the limited observational studies and experimental data of infection in serotine bats, our understanding of the transmission and pathogenesis of EBLV-1 under natural conditions is incomplete. Hence, clinical implications of EBLV-1 infections in serotine bats are discussed. It is clear that *E. serotinus* is known to succumb to clinical infections and therefore is likely to be submitted for rabies diagnosis (Freuling et al.,

2009a). However, reports on EBLV-1 related clinical signs in serotine bats are rare and stem either from animals kept in captivity in bat sanctuaries or experimental studies. Although no information exists concerning the incubation period in naturally infected *E. serotinus* bats, the incubation periods in experimentally infected bats varies depending on the route of inoculation, with the intracerebral route leading to the shortest incubation period (7–13 days), followed by subcutaneous (17–18 days) and intramuscular (26 days) routes (Freuling et al., 2009b). Because intranasal inoculation was ineffective in experimentally inducing clinical rabies, transmission of EBLV-1 among serotine bats via non-bite exposures in nature seems highly unlikely (Johnson, Phillpotts, & Fooks, 2006a). The subcutaneous route of inoculation was relatively efficient in inducing mortality and concomitant shedding of virus in saliva immediately before the development of disease, while intramuscular inoculation was less efficient. Interestingly, experimental intramuscular infection of RABV in Mexican free-tailed bats (*Tadarida braziliensis*) caused fewer virus-positive salivary glands compared with that resulting from subcutaneous infection (Baer & Bales, 1967). From these experimental studies it has been postulated that this may indicate a host-specific adaptation of EBLV-1 and that the subcutaneous route of infection is highly likely to mimic natural transmission among natural hosts via multiple dose infection (Freuling et al., 2009b). In contrast, inoculation of the North American sibling species *E. fuscus* with EBLV-1 by the intramuscular route led to the development of disease in 50% of challenged animals (Franka et al., 2008). Of note, the detection of EBLV-1 infection in infected *E. serotinus* taste buds was observed, mimicking studies with human rabies (Jackson et al., 1999). The significance of this observation, however, remains unclear with respect to potential excretion of virus (Freuling et al., 2009a).

Only a few detailed descriptions are available of naturally EBLV-infected serotine bats and most of these have involved human contacts (Vos et al., 2007). Where clinical disease in naturally infected serotine bats has been observed, animals demonstrated to a lesser or greater degree the following signs: inability to fly, loss of weight, weakness, hypersensitivity for high frequency sounds, prolonged vocalization and uncontrolled wing beats after high frequency sounds, and a strong tendency to bite and react aggressively to stimuli (Anonymous, 1986, 1989; Bruijn, 2003). Experimentally, EBLV-1 causes disease in serotine bats indistinguishable from that observed with RABV infection of North American bats with clinical signs being consistent with those described above (Freuling et al., 2009b). Whether the different EBLV-1 lineages exhibit differences in pathogenicity and result in different disease patterns in serotine bats is currently unknown. The same applies to the recently discovered mutated forms of lineages 1a and 1b possessing either single or hexameric nucleotide insertions within the 3′ untranslated region (UTR)

of the nucleoprotein or 35 nucleotide deletions within the UTR between the glycoprotein (G) and polymerase (L) gene (Freuling et al., 2012a; Johnson et al., 2007). The effects of these changes on viral replication remains elusive, as such mutations had not been previously described for lyssaviruses (Harris et al., 2009).

It appears that *E. serotinus* and *E. s. isabellinus* can survive infection with EBLV-1, as evidenced by the repeated captures of individual seropositive bats over a number of years during serological surveillance initiatives (Harris et al., 2009) and experimental infection (Freuling et al., 2009b). In the latter case, serotine bats surviving in this instance should be considered to have had an aborted infection (Banyard et al., 2011). Although no seroconversion was detected in serotine bats from the Balearic Islands (Spain) and Switzerland (Megali et al., 2010; Serra-Cobo et al., 2002), measurable virus neutralizing antibody (VNA) titers have been detected in free-living con-specifics from several countries with reported prevalences for seroconversion in single colonies in the UK (0.3%) (Brookes et al., 2005; Harris et al., 2009), Germany (5.1%) (Müller et al., unpublished data), in different studies across Spain (4.8%, 7.7%, 19%, and 74%) (Perez-Jorda et al., 1995), and in France (25%) (Picard-Meyer et al., 2011). Similar observations were made in Spanish colonies of *E. s. isabellinus*, where the overall seroprevalence was estimated to be 9% (Echevarria et al., 2001; Vazquez-Moron et al., 2008b). However, in an experimental study, none of the *E. serotinus* infected with EBLV-1 developed VNAs (Freuling et al., 2009b), while in the North American sibling species *E. fuscus* VNAs were detected in survivors and deceased animals (Franka et al., 2008). Although these serological observations in free-living *Eptesicus spp*. have to be interpreted with caution (see the following), this has led some to hypothesize that endemic EBLV-1 is associated with subclinical or mild disease (Vazquez-Moron et al., 2008b). The only experimental study with EBLV-1 in its host reservoir did not provide any evidence for a subclinical carrier state in serotine bats (Freuling et al., 2009b) as repeatedly suggested (Echevarria et al., 2001; Serra-Cobo et al., 2002), and hence the existence of such a state remains to be conclusively demonstrated. The assumption that the clinical expression of EBLV-1 in bats is a non-fatal, extra-neurological infection without important consequences for the health of the *E. serotinus* populations (Echevarria et al., 2001; Vazquez-Moron et al., 2011) is disproved by experimental data and routine rabies diagnostics. Further studies, however, are needed to investigate the circumstances under which neurological manifestations develop in these bats (Vazquez-Moron, et al., 2008a).

2.2.1.3 SEROTINE BATS AS VECTORS FOR EBLV-1

Limited experimental data has shown that other insectivorous bat species, for example, Daubenton's bats (*Myotis daubentonii*), Brandt's bats

(*Myotis brandtii*), common pipistrelle bats (*Pipistrellus pipistrellus*), Egyptian flying foxes (*Rousettus aegyptiacus*), and big brown bats (*E. fuscus*), are susceptible to infection with EBLV-1 (Botvinkin, Kuzmin, & Chernov, 1992; Franka et al., 2008; Kuzmin, Botvinkin, & Shaimardanan, 1994; Kuzmin & Botvinkin, 1996; van der Poel et al., 2000). Because European *Eptesicus* bats are known to cohabit in both mating and wintering roosts with other insectivorous bat species it is not surprising that other bat species have been infected with EBLV-1. Reports of sporadic detection of EBLV-1 in the noctule Bat (*Nyctalus noctula*), the Nathusius' pipistrelle bat (*Pipistrellus nathusii*), the common pipistrelle bat (*Pipistrellus pipistrellus*), the greater horseshoe bat (*Rhinolophus ferrumequinum*), and the particolored bat (*Verspertilio murinus*) (King, Haagsma, & Kappeler, 2004; Müller et al., 2007; Selimov et al., 1991) have been made. Further to this, EBLV-1 RNA has been detected in the Schreiber's bent-winged bat (*Miniopterus schreibersii*); the Natterer's bat (*Myotis nattereri*); the greater horseshoe bat (*R. ferrumequinum*) and the greater mouse-eared bat (*Myotis myotis*) from Spain (Serra-Cobo et al., 2002), indicating that EBLV-1 may circulate in the absence of clinical disease in a range of other bat species under natural conditions. However, whether high EBLV-1 specific seropositivity in free-living bat species such as *M. nattereri*, *R. ferrumequinum*, *M. schreibersii*, and *M. myotis*, and even antigen detection in blood clots in *M. myotis* (Amengual et al., 2007; Serra-Cobo et al., 2002) suggest CST, or evidence of independent reservoirs for these viruses remains questionable.

EBLV-1 is rarely transmitted to terrestrial mammals and humans. Incidents of CST infections of EBLV-1 in sheep, a stone marten (*Martes foina*), and domestic cats have been reported (Dacheux et al., 2009; Müller et al., 2004; Ronsholt, 2002). Furthermore, in contrast to infection with RABV of terrestrial wildlife in Europe, peripheral inoculation of serotine-associated EBLV-1 in terrestrial mammals, including foxes, ferrets, cats, dogs, and sheep demonstrated limited susceptibility of those species (Picard-Meyer et al., 2008; Vos et al., 2004a). The virulence of EBLV-1 is considered to be low with sheep and foxes surviving intramuscular inoculation with a high dose of virus (Baltazar, 1988; Brookes et al., 2007; Cliquet et al., 2009; Fekadu et al., 1988; Vos et al., 2004b).

Although numerous human contacts with serotine bats, primarily from handling sick or injured animals, have been reported (Brass, 1994), only two EBLV-1 induced human casualties have been conclusively demonstrated: in Ukraine in Voroshilovgrad (1977) and in Belgorod, Russia (1985) (Fooks, 2004). Although both cases are known to have involved transmission from a bat to human, the species of bat was not defined for either case. Furthermore, the Russian case was genetically typed as being EBLV-1 while the Ukraine case is only assumed to be EBLV-1 from antigenic profiling (Botvinkin et al., 2005; Selimov et al., 1989). Two further reports of human deaths have been reported following encounters

with bats in continental Europe, although neither has been confirmed as EBLV-1 nor has an involvement of *E. serotinus* been confirmed (Banyard et al., 2011). In conclusion, the probability of serotine bats transmitting EBLV-1 to other species including humans is minimal and there is no evidence that serotine bats will cause EBLV-1 associated epizootics among terrestrial animals or significant human fatalities (Brass, 1994).

2.2.1.4 CONTROL OF SEROTINE BAT-MEDIATED RABIES

In contrast to North Africa and South Asia, where no specific conservation actions are known, across Europe there are internationally recognized legal frameworks in place for the protection of European bats through the Bonn Convention (Eurobats), the Bern Convention, and Annex IV of the EU Habitats and Species Directive. Hence, all bat species are protected by national legislation in member states (Hutson et al., 2008). Therefore, any specific population control measures aimed at reducing disease prevalence in serotine bats is prohibited and from a scientific point of view also unwarranted (Brass, 1994). Rather, in keeping with ongoing conservation measures, the main focus of activities should be on (i) the establishment of adequate surveillance, (ii) objectively increasing public awareness about bat rabies and (iii) targeted pre- and post-exposure prophylaxis (PEP). Although guidelines on passive and active bat lyssavirus surveillance were established and adopted by the United Nations (Anonymous, 2006) and on request from the European Food Safety Authority (Cliquet et al., 2010), it is not clear what affect these guidelines will have on European bat rabies surveillance (Schatz et al., 2012). Vaccination of serotine bats using modified live RABV vaccines as discussed for vampire bats (Aguilar-Setien et al., 2002) is largely unfeasible. Instead, consistent preventive vaccination of all persons working with bats and PEP of all persons with bat exposures should be given as priority as the available human inactivated rabies vaccines stimulate cross neutralizing antibodies and therefore are considered to confer cross protection with EBLV-1, -2 and BBLV (Fekadu et al., 1988; Lafon, Herzog and Sureau, 1986; Malerczyk et al., 2009; Freuling et al., unpublished data). Any media panic and fearmongering that may have a negative impact on serotine bat populations should be avoided.

2.2.2 Lyssavirus Infection of Myotis Bats

As observed with *E. serotinus* and EBLV-1, there appears to be a strong association of EBLV-2 with *Myotis* species. The *Myotis* genus comprises more than 100 species in three main phylo-geographic clades, that is, North America, South America, and the Old World (Lack et al., 2010). In the latter, rabies in Daubenton's bats (*Myotis daubentonii*) and pond bats (*Myotis dasycneme*) has been genetically characterized as EBLV-2.

While the pond bat is confined to Central and Eastern continental Europe, the Daubenton's bat is widely distributed throughout Eurasia (Stebbings & Griffith, 1986) (Figure 6.2B).

In fact, only after the tragic death of a Swiss biologist in Finland in 1985 and subsequent characterization of the causative agent did it become evident that bat rabies in Europe at that time was caused by two different lyssavirus species, EBLV-1 and 2 (Bourhy et al., 1992; Lumio et al., 1986). The first isolation of EBLV-2 from a bat was made in The Netherlands from a Pond bat (Nieuwenhuijs, 1987; Nieuwenhuijs, Haagsma & Lina, 1992). From 1987 to 1993, five Pond bats tested rabies positive, of which the majority were characterized as EBLV-2 (Davis et al., 2005; Nieuwenhuijs, Haagsma, & Lina, 1992). Despite intensive surveillance efforts, no further cases of rabies in the Pond bat were detected in The Netherlands (Van der Poel et al., 2005). All of the Dutch EBLV-2 isolates form a separate cluster, away from the other EBLV-2 sequences (Davis et al., 2005), possibly reflecting geographical or host species relationships. However, since no other *M. dascyneme* associated isolates have been characterized elsewhere and given the distant relationship between these two bat species (Ruedi & Mayer, 2001), it is also likely that cases in *M. dascyneme* resemble CST events from Daubenton's bats. In fact, rabies was also reported from Pond bats in Denmark and Germany (Kappeler, 1989), and Daubenton's bats in Russia. However, the isolates from Denmark and Germany were not characterized, and, surprisingly, isolates from Russia appeared to be RABV, suggesting possible contamination in the diagnostic laboratory (Kuzmin and Rupprecht, 2007).

Elsewhere in Europe, EBLV-2 has been isolated sporadically from the Daubenton's bat in Switzerland (Megali et al., 2010), the United Kingdom (Banyard et al., 2009; Whitby et al., 2000), Germany (Freuling et al., 2012b) and Finland (Jakava-Viljanen et al., 2010). A Daubenton's bat captured during net trapping in Finland showed abnormal behavior, died, and subsequently tested EBLV-2 positive. Molecular characterization then indicated that the first human victim in 1985 had contracted the infection in Finland (Jakava-Viljanen et al., 2010). Besides this Finnish case, a second human rabies case occurred after EBLV-2 infection of a bat biologist in the UK (*Supplementary Case history box 6.1*) (Fooks et al., 2003b; Nathwani et al., 2003). No further EBLV-2 CST events have been reported.

2.2.2.1 NATURAL AND EXPERIMENTAL INFECTION OF MYOTIS SPECIES

As with disease progression seen in natural infection of bats with EBLV-1, the infection of *Myotis* species with EBLV-2 have involved vocalization, agitation, and aggressiveness. Both naturally and experimentally infected bats exhibited a reduced food and water intake a few days before they died (Freuling et al., 2008b, 2012b; Johnson et al., 2006b).

Occasionally, infection of bats has been observed during the rehabilitation of grounded bats in specialist wildlife centers. In such cases, the apparent 'activation' of virus can come following considerable incubation periods ranging from seven weeks (Johnson et al., 2003) to as long as nine months (Pajamo et al., 2008). In comparison, a captive Daubenton's bat infected by experimental subdermal inoculation with a standard dose developed disease after 32 days (Johnson et al., 2008) although numerous alternative routes of infection failed to cause clinical disease.

Following both experimental infection (Johnson et al., 2008) and natural exposure, EBLV-2 RNA was detected in the brain and to a lesser extent in other organs, including the tongue and salivary glands (Banyard et al., 2009; Freuling et al., 2008b, 2012b; Johnson et al., 2003). The heterogeneous pattern in different non-neuronal organs may be linked to the relative time point of death and the degree of centrifugal viral dissemination rather than a specific effect of EBLV-2 (Johnson et al., 2006b).

How EBLV-2 persists in its natural host is still poorly understood. In the UK, where a passive bat rabies surveillance initiative has been established (Brookes et al., 2005; Harris et al., 2009), EBLV-2 specific antibodies are often detected at low levels within bat populations, suggesting that the virus is endemic within the Daubenton's bat population (Banyard, Hartley and Fooks, 2010). Serosurveillance studies have also indicated a low level seroprevalence in the bat population in the UK (Harris et al., 2009), although the mechanisms of persistence at the population level remain unclear. Virus neutralizing antibodies have also been detected in Daubenton's bats in Switzerland and Sweden (Megali et al., 2010; National Veterinary Institute, 2010). It is postulated that transmission of EBLV-2 is through biting or scratching, as virus was detected in oral swabs of a subdermally infected bat in an experimental setting. Furthermore, oral swabs from individual Daubenton's bats from Scotland (2008) and Switzerland (2009) yielded EBLV-2 specific RNA, but not viable virus (Schatz et al., 2012). The perpetuation of EBLV-2 infection in Daubenton's bat populations is driven by virological and ecological parameters (Vos et al., 2007), and rates may confer a virus–host co-evolutionary process. Models indicate that the behavior of the Daubenton's bats result in high gene flow, which may allow EBLV-2 to become established and rapidly spread throughout the population (Smith et al., 2011).

As well as the infection of Myotis bats with EBLV-2, several other lyssaviruses have been isolated from Myotis species. In 1991, an apparently healthy lesser mouse-eared bat (*Myotis blythi*) captured in the Aravan district, Kyrgyzstan, tested positive for rabies by the mouse inoculation test (Kuzmin et al., 1992). In 2001, near the town of Khujand, Tajikistan, a whiskered bat (*Myotis mystacinus*) that was grounded and collected

by hand also tested positive (Botvinkin et al., 2003). Subsequent characterization of the isolated viruses revealed they represent new lyssavirus species Aravan virus (ARAV) and (KHUV) Khujand virus. Little is known about the epidemiology of these lyssaviruses in bats, as only single isolations have been made. Also, as the taxonomy of whiskered bats was modified, it is likely that the bat species from which KHUV was isolated was actually the steppe whiskered bat, *Myotis aurascens* (Benda et al., 2008).

In 2009, a virus isolated from a Natterer's bat (*Myotis nattereri*) from Germany was shown to be antigenically and genetically distant to all previously known lyssaviruses (Supplementary Case history box 6.2), and the virus detected, named Bokeloh bat lyssavirus (BBLV), (Freuling et al., 2011). Natterer's bats are among the species routinely submitted under passive surveillance schemes in Europe, albeit in low numbers (Schatz et al., 2012). It is thus enigmatic why this virus was only discovered recently. Surprisingly, viral RNA (EBLV-1) was previously detected in the brain of a Natterer's bat in Spain, although both fluorescent antibody testing and virus isolation was unsuccessful (Serra-Cobo et al., 2002). Likewise, high levels of VNAs in the greater mouse-eared bat from Spain (Amengual et al., 2007) is only corroborated by viral RNA (EBLV-1) detected in the brain of a few individuals (Serra-Cobo et al., 2002). Elsewhere in Europe, only two cases of bat rabies were confirmed in greater mouse-eared bats, one in Germany and one in Poland (Schatz et al., 2012). Unfortunately, in both instances the viruses involved were not fully characterized. The isolation of closely related lyssavirus species, that is, EBLV-2, ARAV, KHUV, and BBLV from *Myotis* species suggests that this bat genus may play a key role in the transmission and maintenance of this clade of phylogroup I lyssaviruses.

2.2.3 Lyssavirus Infection of Other Insectivorous Bat Species

Alongside the infection of serotine and myotis species there have been a number of individual isolations of lyssaviruses from other bat species. Of these, bats within the *Miniopteridae*, commonly referred to as the bent-winged bats and found across much of Africa, Asia, Australia and southern Europe, have been associated with several highly divergent lyssavirus species. The first lyssavirus to be associated with *Miniopterus spp*. was first isolated in 1970 following the death of a human that had been bitten in South Africa, by an insectivorous bat, while sleeping. The virus was named Duvenhage virus (DUVV) after the individual bitten, and it is thought from the description given that it was most likely a bent-winged bat (Meredith, Prossouw, & Koch, 1971). During the 1980s there were two further reports of DUVV from insectivorous bats. In 1981, the virus was isolated from what was believed to have been a bent-winged bat caught by a domestic cat in Makhado town, Limpopo Province,

South Africa (King & Crick, 1988), although again the species of the infected bat was never confirmed, and in 1986 an Egyptian slit-faced bat (*Nycteris thebaica*) that was trapped during a survey in Zimbabwe also tested positive for DUVV (Foggin, 1988). Another lyssavirus predominantly isolated from African bats, LBV has also been isolated from the insectivorous Gambian slit-faced bat (*Nycteris gambiensis*) (Markotter et al., 2006), although LBV is predominantly associated with the infection of frugivorous bats (see Section 6.4).

Two further human cases involving DUVV have also been reported. The first occurred in 2006 when a 77-year-old man was scratched on the face by an insectivorous bat in North West Province, South Africa. The individual was unknowingly infected and died 14 days following the onset of clinical disease (Paweska et al., 2006). The second case involved the infection of a 34-year-old woman who died 28 days after the onset of clinical disease (van Thiel et al., 2008). The lack of adequate rabies surveillance and characterization of isolates prevents the development of a detailed understanding between lyssaviruses and bats in Africa. Moreover, the number of bat-associated human cases of rabies in Africa remains unknown.

The common bent-wing bat (*M. schreibersii*) became the subject of further interest among rabies scientists when a bat of this species was net-trapped in Russia near the Georgian border and subsequently tested rabies positive for lyssavirus infection (Botvinkin et al., 2003). The virus was only detected conclusively as being a member of the lyssavirus genus following fluorescent antibody testing (FAT) on brain material from mice inoculated with suspect material via the intracranial route that subsequently developed neurological disease. The virus, named West Caucasian bat virus (WCBV), was a genetically divergent bat-derived member of the lyssavirus genus with no serological cross-reactivity to other lyssaviruses (Kuzmin et al., 2005; Franka et al., 2008; Kuzmin et al., 2008b; Horton et al., 2010). Given this observation, neutralizing antibodies against WCBV in *Miniopterus* bats collected in Kenya (Kuzmin et al., 2008b) indicate that WCBV or some other antigenically similar virus also circulates in Africa and in the rest of the Old World where *Miniopterus* bats are abundant (Kuzmin et al., 2011b). The recent discovery of IKOV makes these data even more intriguing, although the serological response to IKOV has not yet been defined with respect to the cross-neutralization of other lyssaviruses.

It is unknown whether the common bent-wing bat is also affected by European lyssavirus species, although EBLV-1 RNA was detected in one *Miniopterus* specimen in Spain (Serra-Cobo et al., 2002). Virus neutralizing antibodies that did not cross-react with WCBV were also found in *M. schreibersii* from France and Spain (Serra-Cobo et al., 2002). A serological survey of bats in the Philippines showed that virus neutralizing

antibodies to Australian bat lyssavirus were most prevalent in *M. schreibersii* (4/11, 36%) (Arguin et al., 2002). However, in none of the 422 bats of this species tested was evidence for an ABLV infection detected (Field, 2004). In any case, the association of *M. schreibersii* with numerous lyssaviruses has led to the suggestion that this species may facilitate cross-continental transmission of different lyssavirus species. This is supported by the global distribution of *M. schreibersii* from southern Europe and Africa and across the Middle East and Caucasus mountains.

Another insectivorous species associated with lyssavirus infection are bats in the subfamily *Murininae*, Genus *Murina*, more commonly known as the tube-nosed bats. In 2002, a bat that had entered an apartment in the town of Irkutsk was captured and died after approximately 10 days with signs of general exhaustion, poor appetite, and weakness. The bat was subjected to rabies diagnostics. Following antigenic and genetic typing, the virus was classified as a lyssavirus and named Irkut virus (IRKV) (Botvinkin et al., 2003; Kuzmin et al., 2005). Initially, the bat was classified as a greater tube-nosed bat (*Murina leucogaster*), although the exact species of the bat from which IRKV was derived remains unclear. A single human case of rabies was reported due to infection with IRKV in 2007, although the bat species involved remains unknown (Leonova et al., 2009).

In 2009, another divergent lyssavirus, named Shimoni bat virus (SHIBV), was isolated from a dead Commerson's leaf-nosed bat (*Hipposideros commersoni*) during a search for pathogens in bats in Kenya (Kuzmin et al., 2010). Antigenically, SHIBV demonstrates similarity to MOKV and LBV, but is genetically divergent from these species (Kuzmin et al., 2010). Additional comparative serological surveys in *Rousettus aegyptiacus* bats and *Hipposideros commersoni* bats in roosts in Kenya where these species sympatrically roost demonstrated that the seroprevalence to SHIBV was equivalent in the presence or absence of *R. aegyptiacus* bats. These data supports the suggestion that *H. commersoni* is the host species of SHIBV (Kuzmin et al., 2011a).

Although initially discovered in and predominantly associated with fruit-eating bat species (see Section 6.3), the Australian bat lyssavirus (ABLV) has also been associated with infection of insectivorous bat species. In Australia, 63 microbat species are detected (Richards, 1998), although ABLV infection has only been confirmed by virus isolation in one insectivorous species, the yellow-bellied sheath-tailed bat (*Saccolaimus flaviventris*). This bat species is a member of the sheath-tailed bats in the family Emballonuridae found in Australia and Papua New Guinea. However, while no further direct isolations have been reported, serological evidence of exposure to ABLV has been shown in seven genera, representing five of the six families of Australian insectivorous bats, that is, *Chaerephon* and *Tadarida* (Molossidae), *Chalinolobus* and *Vespadelus* (Vespertilionidae), *Hipposideros* (Hipposideridae), *Macroderma*

(Megadermatidae), and *Saccolaimus* (Emballonuridae) (Animal Health Australia, 2009). In the latter genus, the yellow-bellied sheath-tailed bat had significantly higher antibody prevalence (up to 62.5%) than other species, suggesting that this bat plays an important role in the ecology of ABLV (Field, 2004). Interestingly, viral antigen was not detected in any of the 668 clinically normal wild-caught microchiroptera collected around Australia; but only in sick, injured, or found dead animals, suggesting that the virus causes disease in bats.

Genetic characterization also revealed that the source of infection in the first human case of ABLV in 1996 was likely *S. flaviventris* (Gould et al., 2002). In a second human case in 1998, subsequent sequence analysis of the viral isolate indicated it was of the variant characteristic of flying foxes (Warrilow et al., 2002) (see Section 6.3).

3 LYSSAVIRUSES AND FRUGIVOROUS BATS

Frugivorous bats belong to the order Chiroptera, suborder Pteropodiformes, superfamily Pteropodidae. Frugivorous bats are present throughout most of the world, performing vital ecological roles such as pollinating flowers and dispersing fruit seeds (Simmons, 2005). Given this broad distribution, the detection of lyssaviruses within only a few species is somewhat surprising (Banyard et al., 2011). The *Pteropodidae* is divided into seven subfamilies with 186 total extant species, represented by 44 to 46 genera. Of these, only a few genera have been directly associated with lyssavirus infection (Table 6.1).

Lyssavirus infection of frugivorous bats is largely restricted to the large fruit bats present across Africa and Australia, with numerous highly diverse lyssaviruses detected. Genetic analysis of isolates by a number of research groups has led to the suggestion that African bat populations are the original hosts for lyssaviruses (Nel & Rupprecht, 2007). However, despite this geographical bias in detection of lyssaviruses in African fruit bat populations, other fruit bat populations across the globe have also yielded different lyssaviruses. Here we describe the principal associations of lyssaviruses with frugivorous bats.

3.1 Detection of Lagos Bat Virus in Frugivorous Bats

From an African perspective, RABV itself is completely absent from fruit bat populations, in direct contrast to the situation seen in carnivores. In place, LBV is the lyssavirus most frequently associated with different fruit bat species. Indeed, LBV or antibodies that neutralise LBV have been isolated from several fruit bat species, including the straw-colored fruit bat (*Eidolon helvum*), Wahlberg's epauletted fruit bat

(*Epomorphorus wahlbergi*), and the Egyptian fruit bat (*Rousettus aegyptiacus*) (Dzkiwi et al., 2010; Hayman et al., 2008, 2010). Studies with African fruit bat species have detected a high seroprevalence of antibodies against LBV in these three different colonial fruit bat species, with antibody levels ranging from 14–67% and 29–46%, for the former two species, respectively. Initial studies showed that older *R. aegyptiacus* and *E. helvum* were shown to have a higher level of seroprevelance within populations of both species (Kuzmin et al., 2008a; Dzikwi et al., 2010; Hayman et al., 2010). Data from *E. helvum* populations derived over a four-year study period demonstrated that seroprevalence in mature bats was significantly greater than that found in juvenile or sexually immature bats. Seroprevalence in sexually mature adults fluctuated between 23% (15–33%) and 49% (39–52%), with no significance seen between the proportion of seropositive sexually mature adults between sampling occasions over the study period (Hayman et al., 2012). Despite significant levels of LBV seropositivity within bat populations, attempts to isolate virus have often been problematic. Indeed, Hayman et al., (2012) tested 796 oral swabs from healthy *E. helvum* using RT-PCR but did not detect viral RNA in any sample. Similarly, Kuzmin et al., (2008a) tested 931 oral swabs and 1,182 brain samples from at least 30 different species of bat by RT-PCR, with LBV RNA only being detected in a single *E. helvum* bat. As expected, high levels of viral RNA were detected in the brain, but also in the salivary gland and tongue, and so salivary excretion was postulated as the means of virus transmission (Kuzmin et al., 2008a). Possible explanations for the seroprevalence levels seen in healthy *E. helvum* bats include: infection with seroconversion and recovery; seroconversion; and latent infection, although no evidence for latent infection has been shown. Further studies are required to enhance our knowledge of how LBV circulates in these bat populations (Hayman et al., 2012).

Both serological and genomic analyses have suggested that LBV isolates form four highly divergent lineages that in some cases are as divergent as some of the other, individually classified lyssaviruses. These have been tentatively termed lineages A to D. Lineage A includes isolates from Senegal (1985) (Swanepoel, 1994), a Kenyan (2007) (Kuzmin et al., 2008a) and a French isolate (either Togolese or Egyptian origin, (1999) (Aubert, 1999); lineage B includes the original Nigerian isolate (1956) (Boulger and Porterfield, 1958); lineage C includes viruses from the Central African Republic (1974) (Sureau et al., 1977), Zimbabwe (1986) (King and Crick, 1988), and South Africa (1980) (King and Crick, 1988) (2003–2005) (Markotter et al., 2006); and lineage D includes a single isolate from Kenya taken from a healthy Egyptian fruit bat (2008) (Kuzmin et al., 2010). The most striking observation from these studies is the close sequence identity of isolates in lineage C that have been reported over

a 25-year period. This suggests a high level of genome stability within these viruses (Markotter et al., 2008).

The detection of LBV in a rabid African water mongoose (*Atilax paludinosus*) was the first isolation of LBV from a terrestrial wildlife species (Markotter et al., 2006). Previous isolations in terrestrial mammals were all from domestic animals, including cats (*Felis catus*) (King & Crick, 1988) and dogs (*Canis familiaris*) (Mebatsion, Cox, & Frost, 1992; Markotter et al., 2008). Alongside the rare detection of natural CST events, the potential for CST events has also, as with other lyssaviruses, been assessed experimentally. Early studies with experimental infection with LBV involved infection of guinea pigs (n=2) and a monkey (*Cercocebus torquatus*) (Boulger & Porterfield, 1958). In these early studies, the virus was reported to be apathogenic and alongside other studies (Badrane & Tordo, 2001) led to the conclusion that phylogroup II lyssaviruses, when inoculated by a peripheral route, were reduced in pathogenicity. Inoculation by the IC route, however, highlighted the ability of both LBV and MOKV to cause encephalitis and death (Tignor et al., 1973). Experimental studies with LBV, MOKV and RABV have suggested comparable mortality following IM inoculation of LBV and RABV, although IM inoculation with MOKV caused reduced mortality (Markotter et al., 2009).

As seen in the epidemiology of RABV and EBLV-1, CST events have also been reported for LBV infection. Indeed, the isolation of LBV from non-volant wildlife species such as mongoose highlights our poor understanding of the incidence and host range of lyssaviruses in Africa. Until molecular tools such as PCR are widely available to assess individual samples, the opportunity to characterize viruses at the molecular level will be missed, a fact highlighted by the detection of a IKOV (Marston et al., 2012). Findings such as this reiterate the need for a thorough molecular analysis of samples to ensure a complete understanding of the epidemiology of these viruses (Fooks et al., 2009).

3.2 Australian Bat Lyssavirus and Flying Foxes

ABLV is predominantly associated with infection of frugivorous flying foxes. Genetic characterization of ABLV detected in *Pteropus* species have shown them to be genetically distinct from those isolated from insectivorous bats, and within each lineage the genetic variation is very narrow (Gould et al., 2002; Guyatt et al., 2003). The initial isolation of ABLV was from a black flying fox (*Pteropus alecto*) in 1996 (Crerar et al., 1996; Fraser et al., 1996). Since then, ABLV has been detected in all four frugivorous bat species present in Australia (Fraser et al., 1996; Gould et al., 1998, 2002; Guyatt et al., 2003). Unlike other lyssaviruses, no correlation has been seen between genetic variation and the

geographical distribution of ABLV isolates within Australia (Gould et al., 2002). Although all flying fox species seem to be affected by ABLV, no species-specific genetic associations have been observed (Barrat, 2004; Guyatt et al., 2003). Interestingly, ABLV is the only lyssavirus species which, from evidence gathered to date, has reservoirs in both mega- and microbats species. The correlation between CST and genetic distances of bat species, as demonstrated for North American bat RABV (Streicker et al., 2010), does not seem to fit as a model for the maintenance and transmission of ABLV. In any case, ABLV appears to be maintained in bat species in Australia. Furthermore, serosurveillance of bat populations in the Philippines and surrounding islands has suggested that lyssavirus infection of bats might be more widespread than previously thought (Arguin et al., 2002), although virus isolations are required due to cross-neutralization between phylogroup I viruses.

From a clinical perspective, the gray-headed flying fox (*Pteropus poliocephalus*) has been assessed for susceptibility to infection with ABLV with the outcome of clinical disease being seen in a proportion of the animals inoculated (McColl et al., 2002). Three of ten intramuscularly inoculated animals developed clinical signs consistent with a lyssavirus infection, but virus neutralizing antibodies were only detected in five of the seven survivors (McColl et al., 2002). In contrast, infection of companion animals with ABLV led to survival in all inoculated cats and dogs, although some animals did show transient neurological signs (McColl et al., 2007). Although no viral antigen could be detected at post mortem in any tissues, strong serological profiles were seen in all infected animals.

3.3 Infection of Fruit Bats with Other Lyssaviruses

With the exception of LBV and ABLV, no other non-rabies lyssaviruses have been detected in frugivorous bats. However, from a molecular perspective, there have been reports of EBLV-1 RNA in Egyptian fruit bats (*Rousettus aegyptiacus*). In 1997, following the transport of a group of Egyptian fruit bats from a Dutch zoo to a Danish zoo, EBLV-1a RNA was detected in not only the exported bats but also within the Dutch colony from which the bats had been exported (Rønsholt et al., 1998). Furthermore, during the investigations surrounding these reports, no clinical disease was observed in any of the bats, and it was concluded that EBLV-1a was being maintained in healthy Egyptian fruit bats (Wellenberg et al., 2002). Following these reports, experimental studies with these bats have shown that, in some instances, these bats are able to survive infection with EBLV-1 following intracerebral inoculation (van der Poel et al., 2000). Further studies are required to understand bat immune responses to lyssaviruses.

3.4 Interaction of Rabies Virus with New World Frugivorous Bats

The frugivorous bat populations of the Americas belong to the Phyllostomidae, and are genetically distant from the true Pteropodidae of the Old World. However, while the fruit bats in the Old World have been associated exclusively with infection of non-rabies lyssaviruses, in the New World the fruit bat populations are only associated with infection with RABV. Pawan (1936) was the first to describe rabies virus infection of frugivorous bats in Trinidad in 1931. This initial report was followed by several other reports of RABV infection of frugivorous bats, including the great fruit eating bat (*Artibeus lituratus*) (Price & Everard, 1977; Stouraitis & Salvatierra, 1978). In these cases, bats were reported to be displaying abnormal behavior and were characterized as being infected with RABV, although it is believed that this infection represented spillover from vampire bat species. Delpietro, Gury-Dhomen, Larghi, Mena-Segura and Abramo (1997) reported that RABV isolates circulating in frugivorous species in South America were antigenically closely related to the vampire bat related viruses commonly described. Shoji et al., (2004) genetically typed a vampire bat rabies variant in *Artibeus spp*. Most recently, complete genome sequencing has shown 97% identity across the entire genomes of a vampire bat derived and a frugivorous bat derived isolate (Mochizuki et al., 2011). Numerous reports across South America detail infection of fruit bats with RABV. But compared to the threat to both human and livestock populations from hematophagous bats (Section 6.4) and the infection of numerous insectivorous bats across the Americas (Section 6.2), the significance of rabies in frugivorous bats in South America is small (Carneiro et al., 2009; Cunha et al., 2006).

4 RABIES IN HEMATOPHAGOUS BATS

Evolution has resulted in one group of bats that are highly effective in delivering a bite capable of damaging the skin and, as a consequence, are highly effective at transmitting rabies to other species: the vampire bats. Many of the biological adaptations of the vampire bat justify this claim, from the dentition that has evolved to cut through the skin of vertebrates, active secretion of saliva containing anti-coagulants to maintain blood flow in a wound, a colonial habit that provides the opportunity for transmission to con-specifics, and a wide selection of prey species that includes humans. For these reasons, vampire bats are a significant cause of death of livestock and responsible for increasing reports of rabies in humans.

Vampire bats are those that derive all their nutrition from feeding on the blood of other vertebrates. Only three genera of bats are blood

feeders or hematophagus. All three belong to the family Phyllostomidae or New-World leaf-nosed bats, and each genus contains a single species (Koopman, 1988). These are the common vampire bat, *Desmodus rotundus*; the hairy-legged vampire bat, *Diphylla ecaudata*; and the white-winged vampire bat, *Diaemus youngi*. The latter species primarily feed on birds, whereas *D. rotundus* feeds primarily on mammals and is responsible for virtually all cases of rabies virus transmission. Therefore, this species will be considered in this section.

Blood-feeding by bats has not evolved outside of Central and South America, and all of the fossil evidence for vampire bats going back to the Pleistocine period (2.5 million years ago to 12,000 years ago) have been found in the Americas (Arellano-Sota, 1988). The association of rabies with the vampire bat is a relatively recent observation, despite the obvious advantage the species has in transmitting rabies. A number of authors have speculated that rabies was present within vampire bat species prior to the Spanish conquest of the New World in the fifteenth century. This is based mainly on the writings of the Spanish colonists (de Oviedo y Valdes, 1950) and the limited information from the indigenous peoples that has survived and been translated (Vos et al., 2011). It is also speculated that the introduction of livestock and horses by the Spanish settlers increased the numbers of potential prey animals and has led to an increase in the population of vampire bats (Greenhall, 1988). A further factor that may have increased both the numbers of vampire bats and brought them into closer contact with humans has been the introduction of manmade structures, such as mines and bridges, that provide additional roosting sites (Greenhall, 1988).

Historically, early writings report rabies as the cause of disease in cattle in southern Brazil following detection of Negri bodies in the brains of cattle (Carini, 1911; Haupt & Rehaag, 1921). However, the link to vampire bats as the cause was not initially accepted, despite the absence of rabid dogs in the affected areas. Later reports, primarily by Joseph Lennox Pawan (1887–1957) on the island of Trinidad, established clearly the link between rabies in vampire bats and outbreaks in livestock in 1925 and humans in 1929 (Hurst & Pawan, 1932; Pawan, 1938). The close proximity between Trinidad and the South American mainland suggested that migration of vampire bats infected with RABV was the likely explanation for the emergence of disease. One of the striking features of these reports was the observation of vampire bat activity during the day and what appeared to be aggressive attacks on humans and tethered livestock (Pawan, 1936).

4.1 Biology of Vampire Bats

The common vampire bat (*D. rotundus*) is widely distributed from northern Mexico to central Chile and northern Argentina. It occupies a

range of ecosystems including rainforests, wetlands, and desert. It is also found at a range of elevations from sea level to 3,500 meters and is not present over much of the Andes and central Mexico (Koopman, 1988).

Common vampire bats roost in colonies of variable size, ranging from less than 10 bats to over 300. Occasionally colonies of 2000 or more individuals have been reported (Arellano-Sota, 1988). Common vampire bats often roost in caves with other species, and both autogrooming and allogrooming are common, potentially providing opportunities for spread of RABV. Furthermore, common vampire bats participate in altruistic feeding, whereby a bat that has fed will regurgitate blood for one that has not. This could provide a further opportunity for transmission of virus.

4.2 Rabies in the Vampire Bat

Pawan (1936) described the appearance of rabies in wild-caught bats. These included both the furious and paralytic forms, as well as sudden death with no apparent disease. Moreno and Baer (1980) conducted the definitive experimental study using RABV prepared from a naturally infected vampire bat. They demonstrated that both intramuscular and subcutaneous inoculation of captive vampire bats resulted in the infection of the bat and that this infection was fatal. Many of the infected bats excreted virus in saliva prior to development of disease but showed no evidence for a carrier status whereby virus could be excreted long-term in a healthy vampire bat. Later studies confirmed the susceptibility of vampire bats to intramuscular inoculation of virus and reported a decrease in blood consumption and dehydration as early signs of infection. Wing and hind limb paralysis was observed (Aguilar-Setien et al., 1998), as well as muscular spasms and tremors (Almeida et al., 2005). Seroconversion was observed in a number of bats that survived inoculation with RABV. A further study observed salivary excretion on three occasions by a small number of bats that survived inoculation with RABV (Aguilar-Setien et al., 2005), although this has not been corroborated by other researchers.

4.3 Epidemiology of Rabies in Vampire Bats

Characterization of RABV in reservoirs in the New World was initially attempted using antigenic differentiation using panels of monoclonal antibodies raised against the RABV nucleocapsid protein (Rupprecht & Dietzschold, 1987; Diaz et al., 1994). This initially classified rabies viruses as those transmitted by terrestrial and non-terrestrial reservoirs and proved useful to identify the source of infection in humans. This has been further developed to distinguish between a variety of antigenic variants, of which there are currently 11 variants that are present across North and South America (Velasco-Villa et al., 2006). This approach to

classification has been further refined through the use of nucleic acid sequence data derived from discrete fragments of the RABV genome. This began with short fragments of the nucleoprotein gene (Smith, 1996), which corroborated the separation of reservoirs based on antigenic variation and allowed further discrimination that began to link particular RABV variants with species (Nadin-Davis & Loza-Rubio, 2006; Franka et al., 2006; Mochizuki et al., 2011).

The main purpose of molecular epidemiology is to trace the variation of RABV in reservoir populations in fine detail. This has been achieved for the rabies virus variants associated with vampire bats, particularly when this has affected cattle (Kobayashi et al., 2006, 2008) or humans (da Rosa et al., 2006; Barbosa et al., 2008; Castilho et al., 2010). The major economic impact of vampire bat predation is through the transmission of rabies to livestock causing death. Estimates have suggested that over a 9-year period losses due to livestock death in the Americas were over $50 million (Belotto et al., 2005). Seasonal peaks in the vampire bat population due to births have been associated with an increase in livestock rabies (Lord, 1992).

Attacks on humans are rare; however, one of the most recent cases of rabies in Louisiana occurred in a migrant worker who was likely to have contracted the disease while in his home state of Michoacán, Mexico (Balsamo et al., 2011). Anecdotal evidence suggests that the incidence of vampire bat attacks on people resulting in rabies is on the increase. This could be due to an actual increase in virus prevalence in the reservoir, or an increase in attacks by vampire bats on humans, or an increase in incident reporting. Changes in human activity have been responsible for increasing vampire predation. For example, removal of livestock can result in increased biting attacks on humans. Many of the reported outbreaks occur in remote communities with limited access to health care professionals and facilities (da Rosa et al., 2006; Goncalves et al., 2002; Schneider et al., 2001).

4.4 Control of Vampire Bats and Future Perspectives

The main approach to the control of RABV transmission has been to control the bat reservoir, mainly through destruction. This takes the form of habitat destruction, that is, destroying roosting caves, or direct trapping and killing of vampire bats (Mayen, 2003). However, this often results in the destruction of other bat species. A more focused approach is the application of anticoagulants, either to cattle (Thompson, Mitchell, & Burns, 1972), or applied directly to captured bats, which are then released. This approach provides a short-term respite but creates an ecological niche that tends to be filled quickly by dispersing vampire bats. Parenteral vaccination of cattle is an effective means of preventing death from rabies infection, although is costly and requires repeated application to every generation. An alternative

to this is oral vaccination with plant-derived feed that has been genetically modified to express RABV glycoprotein (McGarvey et al., 1995; Loza-Rubio et al., 2008). Further investigations have considered vaccination of vampire bats (Aguilar-Setien et al., 1998, 2002). These studies demonstrated that anti-rabies vaccination in the common vampire bat was effective but is costly and unlikely to reach the widespread populations found throughout Latin America.

A further consideration is the potential for vampire bats to increase their range both north into the United States and south to larger areas of Argentina. Climate change models that predict modest increases in winter temperatures suggest that the range of the common vampire bat could spread north into the United States (Mistry & Moreno-Valdez, 2008). Despite their effectiveness at transmitting RABV, there is no evidence for transmission of vampire bat variants to other reservoirs (bats or dogs) with establishment of the variant within the new host and sustained transmission.

5 CONCLUSIONS

In summary, bats have played and continue to play a key role in lyssavirus ecology and evolution. Clearly, many different bat species from different geographical locations and with different feeding habits and ecologies have been found to be infected with different lyssaviruses. However, the unusual distribution of lyssaviruses around the world and their association with particular bat species remains unexplained. Despite the genetic divergence of lyssaviruses detected in different bat species, the disease is similar in all species observed, causing neurological disease where clinical signs are observed. With the exception of vampire bats, the public health risk of rabies in bats remains low, although the consequences of infection are severe. In all species, the mechanisms by which abortive infections occur are unclear. However, there remains no convincing evidence for the existence of a carrier status in bats. While it appears that CST events of lyssaviruses to other mammals, including humans, are rare, the potential for sustained transmission in non-bat hosts exists, although further studies are needed in order to define the many gaps in our understanding of bat lyssaviruses.

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