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European bat lyssaviruses: Distribution, prevalence and implications for conservation

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ABSTRACT

Worldwide, there are more than 1100 species of the Order Chiroptera, 45 of which are present in Europe, and 16 in the UK. Bats are reservoirs of, or can be infected by, several viral diseases, including rabies virus strains (in the Lyssavirus genus). Within this genus are bat variants that have been recorded in Europe; European bat lyssavirus 1 (EBLV-1), European bat lyssavirus 2 (EBLV-2), and four currently unclassified isolates. Since 1977, 783 cases of EBLVs (by isolation of viral RNA) have been recorded in Europe. EBLV-1 or EBLV-2 has been identified in 12 bat species, with over 95% of EBLV-1 infections identified in \textit{Eptesicus serotinus}. EBLV-2 is associated with \textit{Myotis} species (\textit{Myotis daubentonii} and \textit{Myotis dasycneme}). A programme of passive surveillance in the United Kingdom between 1987 and 2004 tested 4871 bats for lyssaviruses. Of these, four \textit{M. daubentonii} (3.57% of submitted \textit{M. daubentonii}) were positive for EBLV-2. Potential bias in the passive surveillance includes possible over-representation of synanthropic species and regional biases caused by varying bat submission numbers from different parts of the UK. In 2003, active surveillance in the UK began, and has detected an antibody prevalence level of 1–5% of EBLV-2 in \textit{M. daubentonii} (n = 350), and one bat with antibodies to EBLV-1 in \textit{E. serotinus} (n = 52). No cases of live lyssavirus infection or lyssavirus viral RNA have been detected through active surveillance. Further research and monitoring regarding prevalence, transmission, pathogenesis and immunity is required to ensure that integrated bat conservation continues throughout Europe, whilst enabling informed policy decision regarding both human and wildlife health issues.

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1. Introduction

In this paper we present an overview of lyssavirus strains that are found in bat species, focussing on European bat lyssaviruses. We will then compare surveillance strategies for lyssaviruses, and in particular those within the UK are discussed. Finally, we will highlight the implications for both bat conservation and human health risks.

In this section of the review, we introduce the order Chiroptera, and the legislation currently protecting bats species...
in Europe. Viral diseases currently recorded in bats, the importance of differential diagnosis and lyssavirus detection methods are also discussed.

1.1. The order Chiroptera and European species

Recent research on the molecular phylogeny of bats places the origins of the Order Chiroptera in the early Palaeocene (64 million years ago) during a period of significant global warming (Simmons, 2005a; Teeling et al., 2005). Of all known extant mammal species, 20% are bats, the only mammals capable of powered flight. Bats are found on every continent except Antarctica, and more than 1100 surviving bat species exist world-wide (Simmons, 2005b). Of the 19 families found worldwide, five are represented in Europe (Vespertilionidae, Rhinolophidae, Molossidae, Emballonuridae, Pteropodidae) (Table 1), with 45 bat species currently listed as European residents including 16 (Myotis myotis is believed to be extinct in the UK as a breeding population) in the UK (EUROBATS, 2004a; Dietz and von Helversen, 2004).

1.2. European bat conservation strategies

The Convention on the Conservation of European Wildlife and Natural Habitats (the Bern Convention) was adopted in Switzerland in 1979, and came into force in 1982, with bats included in Appendix II (all except Pipistrellus pipistrellus) and Appendix III (all species). To implement the Bern Convention in Europe, the European Community adopted Council Directive 92/43/EEC on the Conservation of Natural Habitats and of Wild Fauna and Flora (commonly known as the EC Habitats and Species Directive) in 1992 (Mitchell-Jones and McLeish, 2004). After increasing awareness of the fragile conservation status of bats in Europe, the Agreement on the Conservation of Populations of European Bats (UNEP/EUROBATS) came into force in 1994, under the Convention on the Conservation of Migratory Species of Wild Animals (Bonn Convention/UNEP/CMS). Currently, 30 of the 48 Range States in Europe are parties to the EUROBATS Agreement (EUROBATS, 2004b).

| Family         | Genus      | Number of European species | UK species | UK pop | UK distribution | UK status |
|----------------|------------|----------------------------|------------|--------|-----------------|-----------|
| Rhinolophidae  | Rhinolophus| 5                          | Rhinolophus ferrumequinum | 5000   | SW England and Wales | Endangered |
|                |            |                            | Rhinolophus hipposideros  | 14,000 | Wales, West England and Ireland | Endangered |
| Vespertilionidae| Myotis     | 16                         | Myotis daubentoni        | 150,000| Widespread throughout UK  | Not threatened |
|                |            |                            | Myotis brandtii         | 30,000 | England and Wales | Not threatened |
|                |            |                            | Myotis mystacinus       | 40,000 | Throughout UK – limited in Scotland | Not threatened |
|                |            |                            | Myotis nattereri        | 100,000| Throughout UK | Not threatened |
|                |            |                            | Myotis bechsteinii      | 1500   | Southern England | Endangered |
|                |            |                            | Myotis myotis           | 17     | (1 male found in Sussex, 2005) | Rare |
|                |            |                            | Eptesicus serotinus     | 15,000 | Southern England and South-east Wales | Endangered |
| Nyctalus       | 3          | 3                          | Nyctalus noctula        | 50,000 | England, Wales, Southern Scotland | Endangered |
| Pipistrellus   | 4          |                            | Pipistrellus pipistrellus | 2,000,000 | Widespread throughout UK | Not threatened |
|                |            |                            | Pipistrellus pygmaeus   | 100    | Unknown | Rare |
|                |            |                            | Pipistrellus nathusii   | 200,000| Widespread throughout UK | Not threatened |
| Plecotus       | 5          |                            | Plecotus auritus        | 1000   | Southern England | Rare |
| Barbastella    | 2          |                            | Barbastella barbastellus| 5000   | South of line from The Wash to Wales | Rare |
| Hynpsugo       | 1          |                            |                        |        |                  |           |
| Vespertilio    | 1          |                            |                        |        |                  |           |
| Otonycteris    | 1          |                            |                        |        |                  |           |
| Miniopterus    | 1          |                            |                        |        |                  |           |
| Emballonurida  | 1          |                            |                        |        |                  |           |
| Pteropodidae   | 1          |                            |                        |        |                  |           |
| Molossida      | 1          |                            |                        |        |                  |           |

Data from EUROBATS (2004a), and Dietz and von Helversen (2004).

a The number of European bat species is taken from the EUROBATS (2004a) Protected Species list. The list of countries used to define Europe in this instance, is also taken EUROBATS (EUROBATS, 2004b).

b UK status taken from Harris et al. (1995).

c Myotis myotis is believed to be extinct as a breeding population in the UK.
### 1.3. UK bat legislation

In 1975, the Wild Creatures and Wild Plants Act protected the two most endangered bat species, *Rhinolophus ferrumequinum* and *M. myotis* (Racey, 1992). All bats and their roosts are protected in the UK under the provisions of the Wildlife and Countryside Act (WCA) 1981, which provides the legal framework for bat-related legislation and implementation in the UK for both the Bern Convention (1982) and the Bonn Convention (1985). In England and Wales the provisions of the WCA have recently been strengthened through the Countryside and Rights of Way (CROW) Act, 2000. In addition, the UK ratified EUROBATS in September 1992. Certain bat species are also listed on Annex II (and all species on Annex IV) of the European Habitats Directive. As of July 2004, the UK had recommended 42 maternity and hibernacula areas as Special Areas of Conservation (SACs), and 93 areas as candidate Special Areas of Conservation (cSACs) under the Habitats Directive. Bat species were either the main reason for an area’s recommendation, or a qualifying feature. Implementation of the UK Biodiversity Action Plan (BAP) also includes action for six bat species and the habitats that support them, in the form of Species Action Plans (SAPs) (JNCC, 1998–2005).

### 1.4. Viral diseases found in bats

Ten virus families, including lyssaviruses, have been isolated in bats (Table 2) (Messenger et al., 2003b). There are currently seven virus genotypes (Table 3) in the Lyssavirus genus (family Rhabdoviridae). The genotypes that have been recorded in bats include classical rabies virus (RABV), Lagos bat virus (LBV), Duvenhage virus (DUVV), the European bat viruses (EBLV-1 and EBLV-2) and the Australian bat virus (ABLV). In addition, four viruses that have been isolated from bats are currently awaiting classification in the Lyssavirus genus. These are Aravan virus (ARAV) (Arai et al., 2003; Botvinkin et al., 2003; Kuzmin et al., 2003), Khujand virus (KHUV), West Caucasian Bat virus (WCBV), and Irkut virus (IRKV) (Botvinkin et al., 2003; Kuzmin et al., 2005). Only one Lyssavirus genotype, Mokola virus (MOKV), has never been isolated from bats. Rabies can be caused by any of the genotypes within the Lyssavirus genus. It is a fatal disease of the central nervous system.

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**Table 2 – Virus families and genera associated with worldwide bat genera, and recorded geographical locations**

| Virus family and genus | Bat associated viruses in family | Associated bat genera | Geographical locations |
|------------------------|---------------------------------|-----------------------|------------------------|
| DNA viruses            |                                 |                       |                        |
| Herpesviridae:         | 2                               | 2                     | South America, North America |
| RNA viruses            |                                 |                       |                        |
| Reoviridae:            | 2                               | 2                     | Africa                 |
| Orbitviruses           | 7                               | 10+                   | Africa, North and South America, Australia |
| Togaviridae:           |                                 |                       |                        |
| Alphaviruses           | 1                               | 1                     | North America          |
| Coronaviridae:         |                                 |                       |                        |
| UA*                   | 1                               | 1                     | Asia                   |
| SARS-CoVb             | 1                               | 1                     |                        |
| Flaviviridae:          | 17                              | 15+                   | South America, Africa, Asia, Australia, Europe |
| Flaviviruses           |                                 |                       |                        |
| Negative-stranded RNA viruses | 4 | 3 | Asia, South America, Australia |
| Paramyxoviridae:       |                                 |                       |                        |
| Rhabdoviridae:         |                                 |                       |                        |
| Vesiculoviruses        | 2                               | Multiple genera       | Africa                 |
| Lyssaviruses           | 10                              | Multiple genera       | Europe, Australia      |
| UA*                   | 1                               | 1                     | North America          |
| UA*                   | 1                               | 1                     | Africa                 |
| Orthomyxoviridae:      |                                 |                       |                        |
| Influenza virus        | 1                               | Multiple genera       | Asia                   |
| Bunyaviridae:          |                                 |                       |                        |
| Phleboviruses          | 11                              | 11+                   | Europe, Africa, Asia, South America |
| Arenaviridae:          |                                 |                       |                        |
| Arenavirus             | 1                               | Multiple genera       | North and South America |
| Filoviridae:           |                                 |                       |                        |
| Ebola virus*           | 1                               | 1                     | Africa                 |

Adapted from Messenger et al. (2003b).

a UA – Unclassified to a specific group within the family.
b Li et al. (2005), Lau et al. (2005).
c Swanepoel et al. (1996), Leroy et al. (2005).
Rabies may be suspected when bats exhibit unusual behaviour (aggression (Barrett et al., 2005; Bruijn, 2003; Johnson et al., 2003), apathy, convulsions, staggering, abnormal posturing and arching of the back (Codd et al., 2003). As with viruses, many bacteria can give rise to encephalitis, and therefore altered neurological signs. Little is known about the normal bacterial flora of bats, but pathogenic bacteria have occasionally been isolated. Listerial encephalitis has been mistaken for rabies in cattle in Australia (Animal Health Australia, 2000), whilst other species can also cause meningoencephalitis associated with Listeria monocytogenes has also been seen in fruit bats (Hohne et al., 1975). Brucella species can also cause meningoencephalitis and CNS disease in humans and animals (Sohn et al., 2003), and anti-Brucella agglutins have been found in vampire bats (Ricciardi et al., 1976). Neurological disease has been documented in Australian species of Old World fruit bats caused by the helminth Angiostrongylus cantonensis. Signs included anorexia, hind limb weakness/paralysis, and tetraplegia. Post-mortem examination revealed severe meningoencephalitis (Reddell et al., 1999). Post-mortem diagnosis (including laboratory tests) must therefore be undertaken to exclude notifiable and exotic diseases such as rabies.

In the UK, rabies is a notifiable disease in man (under the Public Health [Infectious Diseases] Regulations 1998) and in other animals (under the Rabies [Control] Order 1974). The Act and Statutory Instruments currently in operation, which control the importation of rabies-susceptible animals are: The Animal Health Act (1981), and the Rabies (Importation of Dogs, Cats and Other Mammals) Order 1974. The Rabies (Control Order) 1974 provides comprehensive powers for dealing with suspected cases (Defra, 2004).

Table 3 – Lyssavirus classification, with geographical origin, original and secondary host species

| Virus                        | Genotype | Geographical origin                | Original host                                      | Secondary host       |
|------------------------------|----------|------------------------------------|---------------------------------------------------|----------------------|
| Classical Rabies Virus (RABV) | 1        | Worldwide*                         | Dog, Fox, Cat, Wolf, Skunk, Raccoon, Mongoose, Bat (America) | Mammals, Man         |
| Lagos Bat Virus (LBV)        | 2        | Nigeria, Africa                    | Frugivorous bat                                   | Cat, Dog             |
| Mokola Virus (MOKV)          | 3        | Nigeria, Africa                    | Shrews, Rodents                                   | Cat, Dog, Man        |
| Duvenhage Virus (DUVV)       | 4        | South Africa, Zimbabwe            | Insectivorous bat                                 | Man (1971)           |
| European Lyssavirus 1a/1b (EBLV-1a/EBLV-1b) | 5 | Denmark, Germany, Netherlands, Poland, Russia, Slovakia, Netherlands, France, Spain | Insectivorous bats (particularly Eptesicus serotinus) | Man (1985)           |
| European Lyssavirus 2a/2b (EBLV-2a/EBLV-2b) | 6 | Netherlands, UK, Finland, Switzerland | Insectivorous bat (Myotis daubentoni, Myotis dasycneme) | Man (1986, 2002)     |
| Australian Bat Lyssavirus (ABL) | 7 | Australia, Philippines | Insectivorous bats (Sacolaaimus fluviiventris) and Pteropus apterus, P. scapulatus, P. conspicillatus | Man (1996)           |
| Aravan (ARAV)                | Unclassified | Southern Kyrgyzstan               | Insectivorous bat (Myotis blythii)                | Unknown              |
| Khujand (KHUV)               | Unclassified | Northern Tajikistan               | Insectivorous bat (Myotis mystacinus)             | Unknown              |
| West Caucasian Bat Virus (WCBV) | Unclassified | Caucasus                          | Insectivorous bat (Miniopterus schreibersii)      | Unknown              |
| Irkut Virus (IRKV)           | Unclassified | Eastern Siberia                   | Insectivorous bat (Miniopterus schreibersii)      | Unknown              |

Modified from Ronsholt et al. (1998).

a Except: Scandinavia, Iceland, UK, Ireland, Australia, New Zealand.

system (CNS) that can affect all mammals, and is an important human zoonosis (c. 55,000 cases worldwide p.a.; World Health Organisation, WHO, 2006), with infection resulting in a wide variety of neurological symptoms. In bats, clinical neurological signs. However, other, non-viral diseases can cause behavioural and/or physical signs in bats similar to those indicative of lyssavirus infection. For example, most recorded injuries to British bats are caused by cats (O’Brien et al., 2005), collision with a vehicle, or roost damage (VLA, unpublished data). Physical trauma to the skull may cause neurological signs such as spasmodic shivering, fasciaccid or complete paralysis (Lane, 1999). Lead poisoning has been documented in fruit bats in Australia (Sutton and Wilson, 1983). Signs presented included severe muscle fasciculation, inability to fly, excessive salivation, ataxia, and making distress noises when approached or handled. Indeed, lead poisoning has been reported in conjunction with ABLV in frugivorous bats and the ABLV initially went undiagnosed because the poisoning was thought to cause the signs presented (Skerratt et al., 1998). However, lead poisoning was also mistaken for rabies in a dog in Australia (Animal Health Australia, 2000). Poisoning by blue-green algae has been reported in bats (WHO, 1998), usually resulting in hepatotoxicity. The toxins include anatoxin-a, a hepatotoxin which leads to convulsions, staggering, abnormal posturing and arching of the back (Codd et al., 2003). As with viruses, many bacteria can give rise to encephalitis, and therefore altered neurological signs. Little is known about the normal bacterial flora of bats, but pathogenic bacteria have occasionally been isolated. Listerial encephalitis has been mistaken for rabies in cattle in Australia (Animal Health Australia, 2000), whilst Listeria induced ‘circling disease’ is common in sheep, and has been seen concurrently with EBLV in Denmark (Ronsholt, 2002; Tjørnehøj et al., 2006). Fatal meningoencephalitis associated with Listeria monocytogenes has also been seen in fruit bats (Hohne et al., 1975). Brucella species can also cause meningoencephalitis and CNS disease in humans and animals (Sohn et al., 2003), and anti-Brucella agglutins have been found in vampire bats (Ricciardi et al., 1976). Neurological disease has been documented in Australian species of Old World fruit bats caused by the helminth Angiostrongylus cantonensis. Signs included anorexia, hind limb weakness/paralysis, and tetraplegia. Post-mortem examination revealed severe meningoencephalitis (Reddell et al., 1999). Post-mortem diagnosis (including laboratory tests) must therefore be undertaken to exclude notifiable and exotic diseases such as rabies.

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2. European bat lyssaviruses (EBLVs) in Europe

In this section, we provide a review of European bat lyssavirus cases (both human and animal), their geographic distribution and implemented surveillance strategies across Europe, including the UK in detail. Other lyssavirus genotypes are also described.

2.1. EBLVs

The presence of EBLVs in Europe was first documented in 1954 (Kappeler, 1989; King et al., 2004), and during the period 1977-2004, 783 EBLV confirmed cases (by isolation of viral RNA) have been reported (King et al., 2004; Müller, 2000; Rabies Bulletin Europe, 2001, 2002, 2003, 2004). EBLV-1 (genotype 5) and EBLV-2 (genotype 6) are related to, but can be genetically and antigenically distinguished from classical rabies (RABV: genotype 1) (Bourhy et al., 1992, 1993, 1999; Badrane et al., 2001). In addition, both EBLVs can be distinguished from each other using sequence analysis of the N and/or G genes (Fooks et al., 2003a).

2.1.1. EBLV-1

EBLV-1 is present in Europe in two lineages, EBLV-1a and EBLV-1b. EBLV-1a is thought to be the most recently introduced from North Africa via southern Spain, and exhibits an east-west European division. The distribution of EBLV-1b appears to follow a north-south division. The Netherlands and France are the only countries in which both EBLV-1a and EBLV-1b have been found (Amengual et al., 1997; Picard-Meyer et al., 2004a,b; Van der Poel et al., 2005). The majority (>95%) of the ~750 EBLV-1 cases in European bats have been identified in one bat species, Eptesicus serotinus (Table 5), which should therefore be regarded as the most likely reservoir species. E. serotinus is found both in the UK and mainland Europe (Stebbins and Robinson, 1992). In the UK, it is found mainly south of a line from The Wash (East Anglia) to south Wales (Hutson, 1991). It is widespread across western Europe, north to Denmark and southern Sweden, south to North Africa, eastwards to the Himalayas and north to Korea, possibly expanding its range in Europe (Baage and Jensen, 1973; Baage, 2001). This species is not commonly migratory, but movements of up to 330 km (200 miles), have been recorded from eastern Europe (Stebbins and Griffith, 1986; Baage, 2001; Strelkov, 1969). Active infection (replicating virus in the CNS and/or excretion of virus in saliva) caused by EBLV-1 has not been recorded in the UK to date, and the disparity between EBLV-1 records in Europe and the UK may be related to the limited geographical distribution and population size of E. serotinus within the UK.

Spillover of EBLV-1 (Table 6) into sheep has occurred on two separate occasions in Denmark, in 1998 and 2002 (Rons Holt, 2002; Tjarnehøj et al., 2004), and into a stone marten in Germany (Müller et al., 2001), a domestic cat (antibodies only) in Denmark (Tjarnehøj et al., 2004) and one confirmed human case (Selimov et al., 1989; Bourhy et al., 1992). A further two unconfirmed human cases of suspected bat origin have also been reported (Table 6) (Rabies Bulletin Europe, 1986; Botvinkin et al., 2004).

2.1.2. EBLV-2

EBLV-2 was first isolated in 1985 from a human, (a Swiss bat biologist) who had been working with bats in Finland, Switzerland and Malaysia (Lumio et al., 1986). In 1986, EBLV-2 was isolated in Denmark and Germany from Myotis daubentonii and in Denmark from M. dasycneme (Table 5), the only known natural

| Table 4 – Lyssavirus distribution in bat tissues for EBLV-1, EBLV-2, ABLV and RABV |
|-----------------|-----------------|-----------------|-----------------|
| Tissue          | EBLV-1 | EBLV-2 | ABLV | RABV |
| Brain           | +      | +      | +    | +    |
| Salivary Gland  | NT     | +      | +    | +    |
| Tongue          | +      | +      | NT   | NT   |
| Pharynx/Larynx  | +      | NT     | NT   | NT   |
| Lung            | +      | +      | NT   | NT   |
| Stomach         | NT     | +      | NT   | NT   |
| Intestine/rectum| +      | +      | NT   | NT   |
| Kidney/bladder  | +      | +      | NT   | NT   |
| Liver           | –      | +      | NT   | NT   |
| Heart           | –      | –      | NT   | +    |
| Testis/ovary    | +      | NT     | NT   | +    |
| Brown fat*      | NT     | NT     | NT   | +    |
| Spleen          | –      | NT     | NT   | NT   |
| Foetus          | –      | NT     | NT   | NT   |
| Wing/skin       | –      | –      | NT   | NT   |

| Tissue          | EBLV-1 | EBLV-2 | ABLV | RABV |
|-----------------|--------|--------|------|------|
| Kidney          | –      | +      | NT   | NT   |
| Foetus          | –      | NT     | NT   | NT   |
| Stomach         | NT     | +      | NT   | NT   |
| Intestine       | NT     | NT     | +    | +    |
| Lung            | +      | +      | NT   | NT   |
| Tongue          | +      | +      | NT   | NT   |
| Brain           | +      | +      | NT   | NT   |
| Pharynx         | +      | NT     | NT   | NT   |
| Pharynx/Larynx  | +      | NT     | NT   | NT   |
| Lung            | +      | +      | NT   | NT   |
| Stomach         | NT     | +      | NT   | NT   |
| Intestine/rectum| +      | +      | NT   | NT   |
| Kidney/bladder  | +      | +      | NT   | NT   |
| Liver           | –      | +      | NT   | NT   |
| Heart           | –      | –      | NT   | +    |
| Testis/ovary    | +      | NT     | NT   | +    |
| Brown fat*      | NT     | NT     | NT   | +    |
| Spleen          | –      | NT     | NT   | NT   |
| Foetus          | –      | NT     | NT   | NT   |
| Wing/skin       | –      | –      | NT   | NT   |

NT, not tested.
EBLV-1: Serra-Cobo et al. (2002) (M. schreibersii, R. ferrumequinum), Echevarría et al. (2001) (E. serotinus), Wellenberg et al. (2002) (R. aegyptiacus), Van der Poel et al. (2000) (R. aegyptiacus), Barrat and Artois, 1998 (E. serotinus).
EBLV-2: Johnson et al. (2003) (M. daubentonii), Johnson et al. (2006b) (M. daubentonii).
ABL: Hooper et al. (1999) (P. scapulatus).
RABV: Nilsson and Negata (1975) (D. rotundus).
a Hibernation link/chronic infection.
### Table 5 – Reported EBLV occurrence in European bat species, with numbers of EBLV positive cases and viruses isolated

| Country                  | Year   | Bat species                  | Number of virus positive bats | EBLV-1/EBLV-2 | References                                      |
|--------------------------|--------|------------------------------|-------------------------------|---------------|-------------------------------------------------|
| Czech Republic           | 1994   | Eptesicus serotinus          | 1                             | EBLV-1        | Matouch (1994)                                  |
|                          | 1999   | Eptesicus serotinus          | 2                             | EBLV-1        | Rabies Bulletin Europe (1999)                   |
| Denmark                  | 1985   | Eptesicus serotinus          | 1                             | EBLV-1        | MMWR (1986)                                     |
|                          | 1986–1987 | Eptesicus serotinus       | 150                           | EBLV-1        | Grauballe et al. (1987)                         |
|                          | 1986    | Myotis daubentoni            | 2                             | EBLV-2        | King et al., 1994                               |
|                          | 1987    | Myotis daubentoni            | 1                             | EBLV-2        | King et al., 1994                               |
|                          | 1998-2001 | Not recorded               | 26                            | Not recorded  | Rabies Bulletin Europe, 1999-2001               |
| France                   | 1989–2002 | Eptesicus serotinus      | 14                            | EBLV-1        | Müllner et al. (2004)                           |
| Germany                  | 1956–2002 | Eptesicus serotinus’    | 147                           | EBLV-1        | Rabies Bulletin Europe (1986)                   |
|                          | 1986    | Myotis daubentoni            | 1                             | Not recorded  | Rabies Bulletin Europe (1986)                   |
| Hungary                  | 1999    | Eptesicus serotinus          | 1                             | EBLV-1        | Rabies Bulletin Europe (1999)                   |
| The Netherlands          | 1984–2004 | Eptesicus serotinus       | 251                           | EBLV-1        | Van der Poel et al. (2005)                      |
|                          | 1984–2004 | Myotis daubentoni          | 5                             | EBLV-2        | Van der Poel et al. (2005)                      |
| Poland                   | 1985–2004 | Eptesicus serotinus        | 53                            | EBLV-1        | King et al. (2004)                              |
| Russian Federation       | 2002–2004 | Unknown                   | 6                             | Unknown       | Rabies Bulletin Europe (2004)                   |
| Slovakia                 | 1998–2004 | Unknown                   | 2                             | EBLV-1        | Rabies Bulletin Europe (2000)                   |
| Spain                    | 1977–2000 | Eptesicus serotinus         | 18                            | EBLV-1        | Echevarria et al. (2001)                        |
|                          | 1992–2000 | Myotis myotis              | 4                             | EBLV-1        | Serra-Cobo et al. (2002)                        |
|                          | 1992–2000 | Myotis nattereri            | 1                             | EBLV-1        | Serra-Cobo et al. (2002)                        |
|                          | 1992–2000 | Myotis schreibersi         | 1                             | EBLV-1        | Serra-Cobo et al. (2002)                        |
|                          | 1992–2000 | Rhinolophus ferrumequinum   | 2                             | EBLV-1        | Serra-Cobo et al. (2002)                        |
| Switzerland              | 1985–2002 | Myotis daubentoni          | 3                             | EBLV-2        | Rabies Bulletin Europe (2002)                   |
| Ukraine                  | 1964    | Eptesicus serotinus          | 1                             | EBLV-1        | Hutson (2004)                                   |
|                          | 1987    | Nyctalus noctula            | 1                             | EBLV-1        | Hutson (2004)                                   |
|                          | 1987    | Vespertilio murinus         | 1                             | EBLV-1        | Hutson (2004)                                   |
|                          | 2001–2004 | Unknown                   | 5                             | EBLV-1        | Rabies Bulletin Europe (2002, 2003, 2004)       |
|                          | 1996    | Myotis daubentoni           | 1                             | EBLV-2        | Whitby et al. (2000)                            |
| UK                       | 2002    | Myotis daubentoni           | 1                             | EBLV-2        | Johnson et al. (2003)                           |
|                          | 2003    | Myotis daubentoni           | 1                             | EBLV-2        | Fooks et al. (2004c)                            |
|                          | 2004    | Myotis daubentoni           | 1                             | EBLV-2        | Fooks et al. (2004b)                            |
|                          | Unknown | Unknown                     | 235                           | EBLV-1        | Hutson (2004)                                   |

Unknown

*Eptesicus serotinus*: 90% of the documented 147 cases were in E. serotinus.

### Table 6 – Spillover cases of EBLVs to non-bat species (including humans)

| Year   | Country | Human/animal species | Viral Infection/Antibodies | EBLV-1/EBLV-2/unknown | References                                      |
|--------|---------|----------------------|----------------------------|------------------------|-------------------------------------------------|
| 1977   | Ukraine | human                | Viral infection            | Unknown, believed to be a EBLV | Rabies Bulletin Europe (1986)                   |
| 1985   | Russia  | human                | Viral infection            | EBLV-1                 | Selimov et al. (1989), Bourhy et al. (1992)     |
| 1985   | Finland | human                | Viral infection            | EBLV-2                 | Lumio et al. (1986), Roine et al. (1988)        |
| 1998   | Denmark | sheep                | Viral infection            | EBLV-1                 | Stougard and Ammendrup (1998)                    |
| 2001   | Germany | stone marten          | Viral infection            | EBLV-1                 | Müller et al. (2001, 2004)                       |
| 2002   | Denmark | sheep                | Viral infection            | EBLV-1                 | Ronsoldt (2002)                                 |
| 2002   | Scotland | human               | Viral infection            | EBLV-2                 | Fooks et al. (2003b), Nathwani et al. (2003)    |
| 2002   | Ukraine | human                | Viral infection            | Unknown, believed to be a EBLV | Botvinkin et al. (2006)                       |
| 2004   | Denmark | domestic cat          | Antibodies                | EBLV-1                 | Tjørnhej et al. (2004)                          |
wild hosts of this virus (apart from a single case in Nyctalus noctula). In total, there are only 18 records of this virus (16 in bats, two in humans) from Denmark, Finland, Germany, the Netherlands, the Ukraine, Switzerland and the UK. Both Myotis bat species (of the eleven Myotis species in Europe, EUROBATS, 2004a) are strongly associated with open riparian habitats, tawling small flying insects from lakes, rivers and ponds. M. dasycneme is confined to central and eastern Europe, from northern-eastern France, the Netherlands and Belgium in the east, southern Sweden in the north and Slovakia to the south (Stebbings and Griffith, 1986; Roer, 2001; Limpens et al., 2000; Roer and Schober, 2001). In the UK, four cases of EBLV-2 have been identified in M. daubentonii (Table 5). Two of the four bats were reported as having bitten humans, and one was reported as being brought into a domestic residence by a cat. Of the four UK cases, two originated in the county of Lancashire (2002, 2004), one in Sussex (1996), and one in Surrey (2004). Both counties of Lancashire and Sussex have submitted a substantially higher proportion of M. daubentonii than other counties for passive surveillance testing. This perhaps indicates that high numbers of bats (of a given species) submitted for rabies testing from specific geographical regions increases the probability of identifying positive cases. Positive results, establishing the presence of EBLV-2 in all four bats’ brains, were obtained by FAT, RTCT and MfT. Identification of the genotyp in each case was undertaken by PCR and sequencing of the nucleoprotein gene and shown to be EBLV-2.

Spillover of EBLV-2 to humans (Table 6) has occurred twice, in Finland in 1985 (Lumio et al., 1986) and in the UK in 2002 (Fooks et al., 2003b). EBLV-2 Spillover into other animal species has not yet been documented.

2.2. EBLV surveillance across Europe

In specific European countries, EBLV infection is currently monitored by passive surveillance of dead or ill bats, using a variety of detection methods (King et al., 2004). In some countries, risk or indicator species are regularly tested where clinical signs are well known and recorded. Table 5 gives the recorded cases of EBLV in bats across Europe by country (where positive cases are documented by laboratory analysis testing for viral RNA in brain or saliva samples).

Financial resources also play a significant role in the scope and surveillance abilities of different countries, with testing density and sample volume being directly affected by financial resources, through the co-financing scheme of the EU (Potzsch, 2004). If the rabies-free status of any European country is to be maintained, then susceptible terrestrial animals must be shown to be both disease- and exposure-free. Effective surveillance is a vital component of any policy that helps to maintain the rabies-free (virus/disease) status of a specific country. The apparent lack of EBLV surveillance in some areas of Europe may be due to classical rabies in fox populations being seen as having greater direct importance, both economically and for public health (Warrell and Warrell, 2004). The WHO defines an area as ‘rabies-free’ where an effective import policy is implemented, and where the area is currently free of indigenous rabies in terrestrial mammals, with no new indigenous case being reported for a period of two years. Currently the Office International des Epizooties (OIE) excludes bat rabies when declaring a country rabies-free (Müller, 2002). During the period 1985–1987, there was a noticeable increase in the number of bats submitted for rabies testing within Europe. The increase in submission numbers of bats, the human case of EBLV-2 in Finland in 1985, and a biting incident involving E. serotinus in Denmark in 1985 (MMWR, 1986) led to EBLV surveillance being taken more seriously.

2.2.1. UK EBLV passive surveillance

Concern that the disease could be introduced into the UK by bats crossing from mainland Europe led to a programme of screening dead bats for the presence of lyssaviruses. This was initiated at the Rabies Research and Diagnostic Unit at the Veterinary Laboratory Agency (VLA: formerly Central Veterinary Laboratory). The passive surveillance programme has been in place since 1987. Dead bats are sent to the VLA by members of the public, or more frequently, by members of the UK’s local bat groups. The annual total of submissions, and the number of submissions for each species between 1987 and 2004, including sex and age ratios are given in Table 6. The average number of bats sent to the VLA each year since 1987 is 270 (range 96–898). However, passive surveillance is likely to have several inherent biases. First, the habitat and colony preference of individual species is thought to have an effect on how frequently they are found by the general public. For example, Pipistrellus species (P. pipistrellus/Pipistrellus pygmaeus) and E. serotinus utilize houses for maternity colonies, increasing the likelihood of grounded adults or young being found. M. daubentonii frequently uses tree cavities during the summer, and caves and mines in the winter, and is therefore far less likely to come into contact with members of the public. This means that some species, when compared to the most recent UK species population estimates, are being under- or over-represented by passive surveillance (Table 8). Second, successful passive surveillance is dependent on bats being recovered from a geographical range that mirrors their natural distribution. In the UK, there are over 90 volunteer bat groups creating a UK wide network, but the activity of these groups and their geographic locations are not necessarily uniform across the UK. Eighty three percent of bats (1987–2004) have been in from England (n = 4041), 8.7% from Scotland (n = 426), 3.5% from Wales (n = 172), with the remaining bats sent from Northern Ireland (n = 15), Republic of Ireland (n = 1), Channel Islands (n = 32), UK offshore (n = 1), and those of unknown origin (n = 185). This has created regions of the UK where very few bats, of few species, have been tested (VLA, unpublished data). Since the detection of EBLV-2 in a M. daubentonii bat in Sussex (1996), the Bat Conservation Trust (BCT) has been working in collaboration with the Department for Environment, Food and Rural Affairs (Defra) and the VLA to promote both the importance of testing bats for EBLVs, and the essential role of the local bat groups. The annual total for bat submission under the passive surveillance scheme have reflected the pattern of UK EBLV cases, with a substantial increase in submissions in the period following each positive case (Harris et al., 2006).

2.2.2. UK EBLV active surveillance

Following the EBLV-2 positive UK bat case in 1996, concern over the potential bias in passive surveillance, and an increased reporting of EBLV in certain bat species in Europe, it
| Year | Annual total | R. fer | R. hip | M. dau | M. bra/M. mys | M. bec | M. myo | M. nat | P. pip/P. pyg | P. nat | E. ser | N. lei | N. noc | B. bar | P. aur | P. aus | Unknown species |
|------|--------------|--------|--------|--------|---------------|--------|--------|--------|---------------|--------|--------|--------|--------|--------|--------|--------|----------------|
| 1987 | 127          | 1      | 3      | 3      | 65            | 1      | 6      | 1      | 6             | 45     | 1      | 2      |        |        |        |        |                |
| 1988 | 349          | 2      | 4      | 12     | 13             | 231    | 3      | 16     | 1             | 8      | 1      | 54     | 4       |        |        |        |                |
| 1989 | 150          | 1      | 1      | 5      | 1              | 3      | 91     | 1      | 6             | 5      | 27     | 9      |        |        |        |        |                |
| 1990 | 398          | 9      | 13     | 12     | 1              | 4      | 1      | 4      | 1             | 1      | 42     | 2      | 4       |        |        |        |                |
| 1991 | 256          | 1      | 4      | 7      | 8              | 177    | 1      | 3      | 3             | 1      | 3      | 50     | 2       |        |        |        |                |
| 1992 | 196          | 3      | 1      | 8      | 6              | 130    | 2      | 2      | 4             | 2      | 38     | 2      |        |        |        |        |                |
| 1993 | 190          | 1      | 8      | 3      | 1              | 132    | 4      | 2      | 31            | 1      | 8      |        |        |        |        |        |                |
| 1994 | 113          | 9      |        | 3      | 7              | 71     | 2      | 3      | 1             | 1      | 3      | 22     | 2       |        |        |        |                |
| 1995 | 96           | 2      | 4      |        | 2              | 67     |        | 2      | 1             | 1      | 18     |        |        |        |        |        |                |
| 1996 | 349          | 2      | 13     | 14     | 10             | 253    | 3      | 4      | 1             | 1      | 46     | 1      | 2       |        |        |        |                |
| 1997 | 188          | 1      | 8      |        | 4              | 141    | 1      | 9      | 1             | 1      | 19     | 4      |        |        |        |        |                |
| 1998 | 157          | 1      | 4      |        | 5              | 114    | 2      | 3      | 1             | 1      | 27     |        |        |        |        |        |                |
| 1999 | 168          | 3      | 7      |        | 4              | 116    | 2      | 4      | 1             | 30     | 1      |        |        |        |        |        |                |
| 2000 | 114          | 1      | 2      |        | 2              | 80     | 1      | 3      | 2             | 20     | 1      | 2      |        |        |        |        |                |
| 2001 | 186          | 2      | 4      | 10     | 1              | 131    | 2      | 3      | 1             | 2      | 25     | 1      | 1       |        |        |        |                |
| 2002 | 186          | 4      | 7      | 5      | 6              | 122    | 1      | 1      | 3             | 37     |        |        |        |        |        |        |                |
| 2003 | 898          | 2      | 6      | 36     | 29             | 40     | 647    | 5      | 9             | 5      | 111    | 1      | 1       |        |        |        |                |
| 2004 | 751          | 14     | 23     | 20     | 14             | 562    | 2      | 9      | 1             | 12     | 1      | 89     | 1      | 3       |        |        |                |
| Species totals | 4871 | 5 | 32 | 112 | 168 | 2 | 1 | 139 | 3439 | 33 | 82 | 9 | 56 | 6 | 731 | 9 | 47 |
| Sex ratio (M:F) | 1:0.81 | 1:0.33 | 1:1 | 1:1.33 | 1:0.97 | 2:0 | na | 1:0.84 | 1:0.78 | 1:1.06 | 1:0.80 | 1:0.5 | 1:0.79 | 1:1 | 1:0.86 | 1:0.33 | 1:0.75 |
| Age ratio (Adu:Juv) | 1:0.88 | 1:0.5 | 1:0.33 | 1:0.68 | 1:0.70 | na | na | 1:2.08 | 1:0.95 | 8:0 | 1:1.25 | 4:0 | 1:0.46 | 1:0 | 1:0.61 | 2:0 | 1:3 |

M. dau, Myotis daubentonii; E. ser, Eptesicus serotinus; M. bra, Myotis brandti; M. mys, Myotis mystacinus; R. fer, Rhinolophus ferrumequinum; R. hip, Rhinolophus hipposideros; M. nat, Myotis nattereri; P. aur, Plecotus auritus; P. aus, Plecotus austriacus; M. bec, Myotis bechsteini; N. noc, Nyctalus noctula; B. bar, Barbastellus barbastellus; P. pip, Pipistrellus pipistrellus; P. pyg, Pipistrellus pygmaeus; P. nat, Pipistrellus nathusii.

Total non-UK resident European species submissions (n = 12).

Myotis dasycneme, Kent 2004 (n = 1).

Pipistrellus kuhlii, Channel Islands 2003, Shipping container 1991, 1995, Unknown origin, 1994 (n = 4).

Pipistrellus savii, Wick, Scotland 1990 (n = 1).

Eptesicus nilsoni, Offshore, 1993 (n = 1).

Tadarida brasiliensis, Maidstone, 1998 (n = 1).

Vespertilio murinus, Offshore, 1992, 2001, 2002 (n = 3).

Myotis lucifugus, Oil Rig, 1992 (n = 1).
became clear that active surveillance and further study into the epidemiology of EBLVs in the UK was required. Therefore, a UK-wide active surveillance programme began in 2003, bringing together experts from the divergent fields of bat ecology and virology (Defra, VLA, University of Bristol [UoB], Central Science Laboratory [CSL], Scottish National Heritage [SNH], University of Aberdeen [UoA], and the BCT).

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Sampling has focussed on *M. daubentoni* and *E. serotinus*, as these are the two main bat species resident in the UK that are known reservoirs of EBLVs in continental Europe, although other species have been sampled in small numbers. The active surveillance sampling tests for both previous exposure (antibody levels), and current infection (viral excretion in saliva). Data generated from two locations (within the counties of Angus and Lancashire) where there was an *a priori* reason to believe that antibody positive bats would be found, gave a prevalence estimate (for *M. daubentoni*) of approximately 8%, with a 95% CI of between 3 and 16%. In contrast, the data from all the other sites in England and Scotland (*n* = 25) suggests that approximately 2% of the *M. daubentoni* population is antibody positive, with a 95% CI of between 1% and 5% (Fooks et al., 2004a; Brookes et al., 2005a).

| Species                  | Species % of total UK bat population | Passive surveillance species numbers | Passive surveillance species % of all bats |
|--------------------------|------------------------------------|-------------------------------------|------------------------------------------|
| Barbastella barbastellus  | 0.15                               | 6                                   | 0.12                                     |
| Eptesicus serotinus      | 0.57                               | 81                                  | 1.68                                     |
| Myotis bechsteinii       | 0.06                               | 2                                   | 0.04                                     |
| Myotis brandtii/Mytotis mystacinus | 2.67                             | 165                                 | 3.43                                     |
| Myotis daubentoni        | 5.72                               | 113                                 | 2.35                                     |
| Myotis myotis            | 0.00                               | 1                                   | 0.02                                     |
| Myotis nattereri         | 3.82                               | 138                                 | 2.87                                     |
| Nyctalus leisleri        | 0.38                               | 9                                   | 0.18                                     |
| Nyctalus noctula         | 1.90                               | 55                                  | 1.15                                     |
| Plecotus auritus         | 7.64                               | 731                                 | 15.2                                     |
| Plecotus australis       | 0.04                               | 9                                   | 0.18                                     |
| Pipistrellus nathusi     | 0.01                               | 33                                  | 0.68                                     |
| Pipistrellus pipistrellus/Pipistrellus pygmaeus | 76.31                          | 3426                                | 71.34                                    |
| Rhinolophus ferrumequinum | 0.15                             | 5                                   | 0.1                                      |
| Rhinolophus hipposideros | 0.54                               | 32                                  | 0.66                                     |
| Total                    | 100                                | 4806                                | 100                                      |

UK species percentage population numbers from Harris et al. (1995).

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From the 52 *E. serotinus* tested by a virus neutralization assay (mFAVN), one sample gave an EBLV-1 positive antibody result (VLA, unpublished data). A longitudinal study (2005 onwards) will enable further sampling and analysis of antibody prevalence within the UK Serotine population. No oral swabs from bats (including those that were antibody positive) of any species tested during active surveillance were found to be RT-PCR positive for viral RNA, and no live virus was detected using RT-CFT (Fooks et al., 2004a; Brookes et al., 2005a).

The detection of virus neutralising antibody in blood samples reflects past exposure to EBLVs only, and does not demonstrate active infection (excretion of virus in saliva) at the time of sampling. The serum data collected 2003–2004, combined with the oropharyngeal swab results may imply that the bats had elicited a sufficient immune response to suppress the virus and might therefore remain sero-positive without excreting virus in saliva. It is probable that bats excreting virus are more likely to show atypical behavioural changes when caught in the field (Johnson et al., 2003). Therefore, not finding EBLV-2 viral RNA in saliva samples from bats that were antibody positive was not unexpected (Brass, 1994). Additionally, the excretion of RABV at least is known to vary with time, an infected animal can excrete virus one day and not the next – so the bat would have to be excreting virus at the time of swabbing for us to be able to detect it. All of the bats that were sampled appeared to be healthy, and were not exhibiting obvious clinical signs of rabies. The majority of the *M. daubentoni* sampled were caught on the wing, another indication of relative good health, considering that active infection in bats may lead to paralysis. The *E. serotinus* sampled were caught both on the wing, and in some cases, taken by hand from their day-roost locations. Therefore, ability to fly was not always observed before sampling of *E. serotinus* occurred.

Further sampling is required on both principal target species (*E. serotinus* and *M. daubentoni*), at both ‘*a priori*’ sites and other sites where there is no reason to expect antibody positive bats.

It is clear that some bat populations (at least *M. daubentoni*) are routinely exposed to lyssaviruses in the UK, and that EBLV-2 has probably been established in the UK for some considerable time. Potentially risks therefore exist for humans and other animals, and an important challenge is to minimize these risks while promoting the conservation of bats. Before addressing how these issues can be reconciled, we will review the distribution of other lyssaviruses in bats, and mechanisms of virus transmission from bats.

### 3. Other lyssaviruses in bats

#### 3.1. Classical rabies (RABV – genotype 1)

Classical rabies was first recorded in insectivorous bats in Brazil in the 1920s (Baer and Smith, 1991) and in frugivorous bats in 1931, in Trinidad (Pawan, 1936a,b), but has never been...
recorded in native European bat species; EBLVs are thought to fill this ecological niche (Table 3).

In North America, the highest prevalence of RABV in wild animals is reported in carnivores (foxes, racoons, skunks), but RABV has been recorded from species in other orders of mammals. The first recording of RABV in North America in an insectivorous bat was in 1951 (King et al., 2004), and since then it has been documented from all over North America (Cliquet and Picard-Meyer, 2004). The annual average prevalence of RABV (viral RNA detection) in bats tested (dead or moribund bats) from nine states of North America between 1988 and 1992 was 7.4% (n = 192/2583). The bat species most commonly submitted are Eptesicus fuscus, Myotis lucifugus, Lasiurus borealis, Lasiurus blassevilli, and Tadarida brasiliensis. The prevalence of RABV infection in submitted bats was lowest in M. lucifugus (1.2%), and highest in L. cinereus and T. brasiliensis, both at 24% (Smith et al., 1995). Surveillance studies indicate a prevalence of rabies virus in <1% of randomly sampled bats (viral RNA detection), and between 3% and 25% among bats submitted to state health departments (Brass, 1994; Schneider et al., 1957; Constantine, 1967a; Trimarchi and Debbie, 1977; Childs et al., 1994; Yancey et al., 1997; Trimarchi, 1998).

Of the total human RABV cases (35 cases during 1958–2000), 19 have been linked with three insectivorous bat species, L. noctivagans (14 cases), Myotis species (two cases) and T. brasiliensis (three cases) in North America. In 1993, three cases of rabies of probable bat origin in red foxes Vulpes vulpes were confirmed on Prince Edward Island (Canada) (Daoust et al., 1996). In 2001, 19 skunks from Arizona sent for rabies testing to the Texas Department of Health were found to be infected with a RABV variant more commonly identified in E. fuscus and Myotis species (Smith, 2001).

In Latin America, Desmodus rotundus, the common vampire bat, is thought to be the principal reservoir of RABV infections in humans (500 cases during 1975–2000) (McColl et al., 2000). Cases of human RABV infection resulting from vampire bat species may be under-reported in Latin America, but several outbreaks have been recorded (Uieda et al., 1998; Milagres, 2005; Rodriguez, 2005). Attacks by vampire bats appear to occur most frequently in areas of human settlement (Caraballo, 1996; Schneider, 1991; Schneider et al., 1996; Schneider and Uieda, 1998), or when normal food sources are not available, such as following the removal of pigs during a hog cholera eradication campaign (McCarthy, 1989). RABV of vampire bat origin in cattle is of economic concern, but has also led to significant losses of both habitat and bat species through ill-conceived bat control programmes.

3.2. Lagos bat virus (LBV)

Lagos bat virus (LBV – genotype 2) was first isolated from the brain of the straw-coloured bat (Eidolon helvum) in 1956 (Lagos Island, Nigeria) (Boulger and Porterfield, 1958), and has since been isolated from the same species in Senegal, in 1980 (Table 3). It has also been reported in other bat species for which limited information is available including Epomophorus wahlbergi and an unidentified bat species (both from the Natal Province, South Africa), Micropteropus pusillus (Central African Republic), and Nycteres gambiensis (Guinea). The case identified in E. wahlbergi in South Africa involved a rabies-like outbreak involving many bats of that species. Lagos bat virus has also been isolated from cats (Zimbabwe and Natal) and a dog (Ethiopia). There is no record of human infection (Brass, 1994). In addition to these records, isolation of the virus was reported from a bat imported into France from either Togo or Ethiopia in 1999 (the origin of the bat was unconfirmed). The bat was recorded as a Pteropus species, but this genus does not occur on mainland Africa, and therefore was believed to have been mis-identified (Aubert, 1999; Hutson, 2004).

3.3. Mokola (MOKV – genotype 3)

Mokola virus was first isolated in 1968 in Nigeria from a shrew, and has since been recorded again from a species of white-toothed shrew (Crocidura species) (Cameroon), and once in the brush-furred mouse (Lophuromys sikapusi) (Central African Republic) (Table 3). Apart from these cases, the virus has been isolated from several domestic cats and a single dog in Zimbabwe. There have been two reported human cases both from Nigeria, one fatal, and the other case was believed to have been misdiagnosed (Brass, 1994). Mokola virus is believed to be widespread, but uncommon is West Africa, Central Africa, Ethiopia, Zimbabwe and South Africa (Bingham et al., 2001). The virus has not been recorded in any bat species, however they have been considered as a potential reservoir host (Shope et al., 1970; Brass, 1994).

3.4. Duvenhage Virus (DUVV – genotype 4)

Duvenhage virus was first isolated in 1970 (Table 3), in Transvaal, South Africa, from a fatal human case (Meredith et al., 1971). This was believed at the time to have been caused by a bite from an insectivorous bat (either Miniopterus schreibersii or Miniopterus schreibersii natalensis), although the evidence for the bat bite has since been seen as circumstantial (Van der Merwe, 1982). The virus has subsequently been isolated from an unidentified insectivorous bat species (Transvaal, Africa in 1981) and from a Nycteris thebaica (Zimbabwe in 1996) (Brass, 1994).

3.5. Australian bat lyssavirus (ABLV – genotype 7)

In 1996, ABLV was first isolated from a Pteropus alecto bat in New South Wales, Australia (Table 3), and two human deaths were also reported in Australia that year (Allworth et al., 1996; Hanna et al., 2000). During this time, ABLV was also isolated from two further fruit bat species (P. scapulatus and P. poliocephalus), and from an insectivorous species (Saccolaimus flaviventris). In 2000, contact between a wild P. alecto and a captive P. poliocephalus separated by wire-mesh resulted in transmission of ABLV. Subsequent modification of the enclosure prevented future direct contact between free-living wild bats and the captive colony (Warrilow et al., 2003). Evidence of infection has been recorded in bats in all states except South Australia (Fraser et al., 1996; Tidemann et al., 1997; Hooper et al., 1997; Gould et al., 1998; Samaratunga et al., 1998). A survey involving 119 bats linked with potential human contact cases, including various Pteropus species (n = 85) and nine insectivorous species (n = 34), found eight positives (by FAT)
in Pteropus species, (prevalence estimate of 9.4% in submitted bats) and no positives, in the other species. Opportunity for cross-species transmission of ABLV involving pteropodids may be partly facilitated by the large, seasonal, nomadic and sometimes multi-species colonies in which they are known to congregate (Warrilow et al., 2003).

In the Philippines, active surveillance of bats during the 1950s and 1960s failed to record active rabies infection, although surveillance in 1998 found a 9.5% ABLV antibody prevalence (n = 231), but no active infection (Arguin et al., 2002). Active surveillance in Thailand found an antibody prevalence to ABLV between 4% and 7.3% (n = 394), (Lumlertdacha et al., 2005).

4. Lyssavirus transmission

In this section we provide evidence for EBLV tolerance in bats, and discuss forms of transmission of EBLV from bats to humans. The apparent differences in virulence between Lyssavirus genotypes for different animal species will also be considered.

4.1. Evidence of EBLV tolerance in bats

There is an increasing body of evidence to suggest that bats tolerate lyssavirus infection. A study following the unexplained infection of a captive colony of Rousettus aegyptiacus with EBLV-1 (Ronsholt et al., 1998), demonstrated that though the virus was pathogenic for the bat, this species could survive challenge with this virus (rabies antigen and neurological signs were detected in six out of seven of the 16 inoculated bats) (Van der Poel et al., 2000). Further studies revealed that up to 85% of apparently healthy colony members (n = 43) were seropositive for EBLV-1, indicating exposure to the virus (Wellenberg et al., 2002). In a recent study, the EBLV-1 RNA was detected in a range of tissues from apparently healthy specimens of M. myotis, Myotis nattereri, R. ferrumequinum, and Myotis schreibersii. In the same study, neutralising antibodies were present in M. myotis, M. schreibersii, Tadarida teniotis and R. ferrumequinum (Serra-Cobo et al., 2002). These studies corroborate investigations of bats endemic to Europe, which demonstrated, by repeated humane blood sampling of selected bat colonies, that the same seropositive individuals could be detected over a six-year period. This illustrates that bats may survive EBLV infection with possible long-term maintenance of virus in infected healthy individuals (Perez-Jorda et al., 1995; Echevarria et al., 2001; Serra-Cobo et al., 2002; O'Shea et al., 2003, 2004).

However, it is not clear how EBLVs are transmitted between bats within a colony. The complex social behaviour of bats, sometimes including allogrooming (Kerth and Konig, 1999) may possibly enable virus dissemination through the sharing of saliva. It is speculated, however, that the mechanisms of EBLV transmission via the oral route and the level of viral load involved may result in a ‘silent’ (no obvious clinical signs) infection. The possibility exists that bats might act as ‘asymptomatic viral carriers’ resulting in a sub-clinical infection. Virus re-activation may also occur as a result of specific ‘stress’ factors including pregnancy, hibernation, nutritional deficit, and migration, that cause immunosuppression and potentially increase rabies-related mortality (Sulkin et al., 1959, 1960; Sims et al., 1963; Constantine, 1967a,b). Previous work (Soave, 1962, 1964) has shown that even after long periods of asymptomatic infections, guinea pigs developed clinical rabies when subjected to stress (Messerger et al., 2003a). In contrast, as part of complex bat behaviour, biting incidents that may result in viral transmission are fairly common. Transmission could be followed by abortive peripheral infection via lack of virus replication or the development of sterilising immunity. Alternatively, the virus replicates locally, is transmitted to the CNS and fatal infection ensues. In 2001, a captive colony of 35 E. fuscus was created from wild-caught bats and held for just under five months to study the epidemiology and transmission of the classical rabies virus (RABV). Within the first month of capture, two bats died, and were found to be positive for RABV by RT-PCR of brain tissue, salivary gland and oral swabs. Of the remaining bats, all remained outwardly healthy, with two bats seroconverting whilst in captivity. Five other individuals that had been seropositive for RABV before capture, maintained their positive antibody levels (Shanker et al., 2004).

4.2. Cryptic transmission of bat lyssaviruses to humans

Cryptic transmission (cases where a clear history of exposure to rabies cannot be documented) of RABV bat variants to humans in the Americas is thought to occur once or twice each year; often the bite goes unrecognised (Jackson and Brock Fenton, 2001; Messenger et al., 2002, 2003b). It is feasible that in Europe viral encephalitis currently of unknown aetiology might occur following exposure as a result of a bite from an EBLV-infected bat (Smith et al., 2005; Davison et al., 2003).

In the majority of cases of human rabies infection the source is a bite wound. In some cases however, infection may result from the virus coming into contact with mucous membranes (e.g. eyes, nose and mouth). There are four reported instances of human rabies following inhalation of aerosol virus, two cases in a laboratory (Winkler et al., 1973), and two in a bat cave (Gibbons, 2002). However, it cannot be shown conclusively, particularly with the cave infections, that there were no other means of infection, as one of the cavers involved was reported as having an open wound on his face (Constantine, 1962, 1988a,b; Brass, 1994; Gibbons, 2002). However, airborne transmission of Lyssaviruses has been demonstrated experimentally (Johnson et al., 2006a). There are also a small number of cases of fatal human rabies infection in recipients of donated organs (Hough et al., 1979; Srinivasan et al., 2005; Hellenbrand et al., 2005).

4.3. Direct (salivary) transmission of EBLVs

The potential for direct transmission of lyssavirus is indicated by the presence of virus in the salivary glands, tongue and pharynx. These organs appear to be the most significant in relation to the most common forms of virus spread; bite, lick (or broken skin) or contact with mucous membranes. All three confirmed human cases of EBLV documented previous exposure to bat bites. The human case of rabies caused by EBLV-1 reported a specific biting incident from a single bat. The two human cases of rabies caused by EBLV-2 reported
multiple exposures to bats involving biting incidents. It is possible that EBLV transmission may occur infrequently due to low levels of virus in saliva, poor invasive ability of EBLVs, or immune status of those bitten (Fooks et al., 2003a). This suggests that bat to human spread of EBLVs may require a significantly higher viral load before an active infection is established compared to the virus load received from a dog bite. However, the extent and depth of exposure (physical area of exposure and amount of saliva) in dog bites is generally much greater than that of bat bites.

4.4. Degrees of lyssavirus virulence

In a comparison of two RABV isolates (a L. noctivagans isolate taken from a naturally infected human from California, and a coyote street virus isolate taken from a naturally infected coyote from Texas) from North America, the isolate from L. noctivagans replicated to higher titre levels in epithelial and fibroblast cells at cooler temperatures (34 °C) (Dietzschold et al., 2000; Morimoto et al., 1996), potentially facilitating more effective local replication in the dermis, even after a seemingly superficial bite by this bat species. This type of situation, where a species has evolved genetic changes associated with enhanced viral infectivity, has been described as the increased infectivity hypothesis (Messenger et al., 2003a), although currently this theory remains largely unproven (Hughes et al., 2005). Between EBLVs, a difference in pathogenicity is believed to occur, with EBLV-1 being potentially more virulent than EBLV-2, with all reported spillover infections in terrestrial (non-human) mammals being of EBLV-1 origin. Recent studies have indicated that foxes (Vos et al., 2004a), cats, mice and ferrets are more susceptible to EBLV-1 infection than EBLV-2, (Vos et al., 2004b), as is also the case in murine models (Brookes et al., 2005a,b). No spillover hosts have been reported for ABLV; recorded human infections have been caused by direct exposure to infected bats (MacKenzie et al., 2003). ABLV infection has not been identified in either domestic or wild (non-bat) mammal species (McColl et al., 2000; MacKenzie et al., 2003), suggesting that the virus cycles only in bats. ABLV susceptibility studies have initially found that both cats and dogs infected experimentally do seroconvert, and in some cases, exhibit clinical signs (MacKenzie et al., 2003).

5. Discussion

In the final part of this review, we discuss the effects of rabies control measures on bat populations, with both positive and negative outcomes, in relation to biodiversity and conservation. The importance of education and awareness is discussed, especially regarding current policy and advice for bat research workers.

5.1. Lyssaviruses as a threat to bat species

There is sparse evidence for accurate assessment of the impact of rabies on bat populations. Knowledge of EBLV epidemiology and prevalence is limited. Few large-scale die-offs of bats have been reported (CDC, 1964; Clark et al., 1996), and rabies was not officially confirmed as the primary cause of death in these (Constantine, 1967a,b). Difficulty in quantifying die-offs may come from a lack of knowledge of baseline population size and mortality rates in wild animals. Adequate knowledge of the behavioural ecology of any rabies vector species, especially those such as bats, as endangered and/or protected species, is integral to the successful management of rabies (Macdonald, 1993). This highlights the need for increased research into the epidemiology of bat rabies, and population studies of potential or known host species, combined with an increase in surveillance.

5.2. Rabies control measures

Rabies control measures and associated management strategies for bats remain limited, partly due to the high mobility of bats. Management is frequently aimed at public awareness and habitat modification, such as the exclusion of bats from a particular building (Frantz and Trimmerchi, 1983; Greenhall, 1982). This however, can be difficult to achieve, and unnecessary if contact can be minimised by other means. A study in Spain identified an antibody prevalence to EBLV-1 of 7.8% (Serra-Cobo et al., 2002) in bat colonies in areas frequently visited by members of the public. The entrances to the caves in which the colonies live are now grilled, human access is controlled and limited during periods of bat habitation.

In Latin America, an estimated 0.15% of 70 million cattle are lost each year due to vampire bat-related rabies, costing the economy $US30 million dollars per year (Acha and Arambulo, 1985). Vampire bat control programmes have produced ill-conceived and indiscriminate methods for reducing populations (Acha and Arambulo, 1985; Greenhall and Schmidt, 1988), with techniques such as firearms, electrocution, smoke, flame-throwers, dynamite, poison gas, and Newcastle disease as atomised virus used to destroy individuals and roosts (Hutson et al., 2001). These methods may produce short-term reductions in the prevalence of rabies in cattle, but risk the geographical dispersal of disease through forcing bats to move from disrupted roosts into areas where perhaps rabies was not previously a problem (Fooks, 2004d). Bat Conservation International (BCI) has implemented education programmes regarding management of vampire bat populations, in an attempt to promote efficient, species-specific control (Lord, 1988). Experimental RABV vaccination of a captive vampire bat species (D. rotundus) indicated that oral vaccination methods (more suited to potential field vaccination programmes) produce lower rates of sero-conversion than intra-muscular (IM) routes (Aguilar-Setien et al., 1998, 2002).

In Europe, alternative management strategies, such as vaccination against rabies of domestic dogs in Denmark (Pedaku et al., 1988; Racey, 1992) should be viewed as positive conservation efforts, taking into consideration both bat conservation and human health, protecting bat populations whilst protecting people. The current risk of EBLV spill-over from bats to other organisms in Europe is believed to be low, in comparison with RABV spill-over in both North and Latin America, where outbreaks of bat variant RABV have been reported in striped skunks (Mephitis mephitis) in Arizona (Smith et al., 2001) and detected (by monoclonal antibody screening) in other mammal species such as cats, dogs, cattle, horses, sheep and foxes (Messenger et al., 2003a).
5.3. Consequences for biodiversity

Control methods such as those used for vampire bats may have impact on other non-target bat species (Hutson et al., 2001), and in turn affect biodiversity at a local, if not wider scale. In Venezuela, from 1964 to 1966, an estimated 900,000 bats of various species were gassed annually as part of vampire bat control programmes. Losses of non-target bat species are also thought to have occurred due to the barricading of caves (Pint, 1994), selective burning of trees, and application of anti-coagulant paste (McCarthy, 1978) on randomly caught bats. The potentially detrimental effect of actions such as these upon the local ecosystem, and the effect on bat species diversity have not yet been studied in detail (Hutson et al., 2001). The control of vampire bat populations, in relation to the protection of domestic livestock and humans, may be necessary in certain geographic regions. However, the main aims of any control strategy should be first, to regulate the population levels of the target species regions. However, the main aims of any control strategy should be first, to regulate the population levels of the target species (rather than indiscriminate destruction of individuals) and second, to ensure protection of non-target species, to maintain species diversity (Greenhall, 1968; Lord, 1988).

5.4. Attitudes and education: conservationists and the general public

The conservation of bats in certain areas of the world has been significantly affected by human perception of their potential as vectors and transmitters of lyssavirus (McCracken and Rupprecht, 2004; Mickleburgh et al., 1992, 2002; Temby, 2004). This, in turn, may result in habitat and/or roost loss, due to reduced tolerance of bats in proximity to human dwellings. Occupational exposure is a potential risk, for groups such as bat researchers, bat care workers/rehabilitators, builders, fishermen, arborists and vets. Education efforts reflecting scientific advice regarding the human health risks associated with bat rabies are essential. Risks to the general public remain minimal, but the fatal consequences of rabies mean that the hazard must be taken seriously. Continuity across countries, regarding handling methods (gloves), vaccination (compulsory or highly recommended) and treatment after potential exposure, are all integral in creating a Europe-wide agreement on management and conservation of bat populations (Racey and Fooks, 2005). Prophylactic vaccination is recommended for those professionally or recreationally exposed to bats in most European countries. Within the UK, there are a number of organisations concerned with bat conservation (e.g. BCT, Mammals Trust UK, Mammal Society, Scottish Natural Heritage (SNH)), that now have the additional role of advising their members and the general public on bat lyssavirus issues.

During the past 15 years, the number of confirmed cases (virus positive) of EBLV in Europe has increased in direct association with an increase in surveillance. Bat-associated rabies cases are likely to be under-estimated globally due to lack of reporting or recording of bat related occurrence and/or the lack of rabies isolate typing. The EBLV-2 lyssavirus strain is thought to have been present in the UK for a considerable time (Racey and Fooks, 2005), but the potential spread and infection within bat populations, and the perceived health risk to humans are newer, more immediate issues, requiring surveillance, research and education to enable bat conservation to continue worldwide in a realistic and informed manner. Surveillance programmes for EBLVs throughout Europe and the UK play an integral role in developing a greater understanding of both the transmission and prevalence of the disease. Integrated with this should be research on bat behaviour and movement patterns, to enable the relationship between disease and host to be fully understood.

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