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## Reassessing the risk from rabies: A continuing threat to the UK?

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### ABSTRACT

The threat of re-introduction of rabies virus into the United Kingdom exists on several levels. Firstly, importation of live animals into the UK continues to challenge the regulations in place to ensure that the virus does not enter the country. Secondly, the indigenous bat population is known to carry a virus genetically related to rabies virus, the European bat lyssavirus (EBLV). Molecular characterization of this virus has further characterized it as being EBLV type 2, genetically distinct from a similar virus that has caused several human deaths across Europe. Finally, a lack of awareness of the threat of rabies and related viruses to travelers visiting endemic areas also constitutes a re-introduction threat to the UK population. This review will address the most recent cases of lyssavirus infection, in both humans and animals, either contracted within the UK or from abroad. We highlight the current diagnostic necessity for testing indigenous and foreign cases and comment on current UK government policy in light of a European call to harmonise rabies legislation across Europe.

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### 1. Introduction

To the developed world, rabies remains a largely neglected disease. Highly efficacious vaccines are available and in the event of an unvaccinated individual becoming exposed, prompt application of recommended procedures prior to clinical disease will avoid fatalities. The UK has had a rabies-free status for over 100 years, maintained by bio-security measures, rigorous public health management systems and more recently through the implementation of the Pet Travel Scheme (PETS) with retention of quarantine rules, in existence since 1901, for non-PETS animals. Even with these measures in place, the threat of re-introduction of the virus still exists on three levels. Firstly, the legal and illegal importation of live animals into the UK poses a threat, especially with the increased movement of human populations from areas of endemicity both within Europe and outside of the European Union (EU) into the UK. Secondly, the indigenous bat population is known to carry a virus genetically related to rabies virus, the European bat lyssavirus (EBLV). Molecular characterization of this virus has further classified it as being EBLV type 2, genetically distinct from a similar virus (EBLV-1) that has caused several human deaths across Europe.

EBLV-2 has caused one death in the UK in 2002, where a bat worker succumbed to infection following exposure(s) to a bat(s) infected with EBLV-2 (Fooks et al., 2003c). This isolated case led to

a renewed interest in these viruses with extensive media coverage fuelling concerns over the threat of these viruses to the public, and in particular, the role of bat species as reservoir hosts. Finally, a lack of awareness of the threat of rabies and related viruses to travelers visiting endemic areas also constitutes a re-introduction threat to the UK population. Unfortunately, human tragedy is often required to raise public awareness to the threat of zoonotic disease. The tragic case of a young Irish woman succumbing to infection with rabies virus in 2009 once again raised the public profile of rabies within the UK, although this was not the first time that infection with rabies virus has been brought to public attention in recent times (Johnson et al., 2002; Fooks et al., 2003c; Hunter et al., 2010).

This review will address the most recent UK cases of lyssavirus infection, in both humans and animals, either contracted within the UK or from abroad. We highlight the current diagnostic necessity for testing indigenous and foreign cases and comment on current UK government policy in light of a European call to harmonise rabies legislation across Europe.

### 2. Rabies in the UK: history and current legislation

Historically, rabies is one of the most feared viruses of man. Late stage disease often includes aggression, delirium, convulsions and invariably death, the imagery behind public perception of the disease. The discovery of a number of related viruses, almost all isolated from bat species across the world, has seen the interest in this small group of viruses increase within the scientific community. Of course the island nation status of the UK has enabled

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freedom from this terrifying disease for decades. In the 19th century rabies was widespread in the United Kingdom. The disease was maintained in packs of stray dogs with wildlife involvement remaining unreported. In the period 1886–1903 there were 3056 cases of dog rabies and more than 160 human deaths (Fooks et al., 2004a). The 'General Rabies Order', 1897 gave powers to the Board of Agriculture to enforce muzzling of dogs in specified districts and destruction of strays. These measures were highly effective with the last indigenous case occurring in Wales in 1902 (Fooks et al., 2004a).

### 2.1. Quarantine measures

To prevent recurrence of widespread disease, the Importation of Dogs Act of 1901 required imported dogs to be isolated at an approved kennels for a period of six months. Official quarantine measures were tightened further for dogs in 1922 and cats in 1928. The purpose of quarantine was so that rabies can be detected, contained and eliminated in controlled conditions with minimal risk of transmission to humans, domestic animals and wildlife. This stringent disease control method has been highly effective in protecting both the human and animal populations of Britain from rabies. Since 1922, there have been twenty-seven cases of rabies that have been confirmed and controlled (Fooks et al., 2004a). In 1969, a dog imported from India died of rabies in quarantine and in the same year two dogs, which had been released from the same quarantine station as the original dog, also died. This led to the introduction of the administration of rabies vaccine to all animals either prior to or on entering quarantine (Fooks et al., 2004a).

Since the introduction of quarantine rules there has only been one outbreak of rabies. This occurred between 1918 and 1922 originating from dogs smuggled into the country by returning First World War servicemen. Three hundred and twelve dogs, eight cattle, two sheep, three pigs and three horses were infected. Rabies was eliminated through muzzle and leash restrictions and the destruction of stray dogs (Fooks et al., 2004a). This outbreak demonstrated the importance of border controls and enforcement of import restrictions from countries with high levels of endemic disease.

Seventy-five years after the introduction of quarantine for pet animals, in 1997, the UK government initiated a review of the use of quarantine rules recognising that other countries such as Sweden and Australia were utilising alternative systems successfully. An enquiry chaired by Professor Ian Kennedy published a report 'Quarantine and Rabies – a reappraisal' in 1998 making 41 broad recommendations. In response to this, new legislation was developed that established the PETS scheme.

There remains complex legislation and a network of enforcement agents that continue to protect the UK from this most serious disease. The main domestic provisions are provided by 'The Rabies Importation of Dogs, Cats and Other Mammals Order 1974' which implements a number of European directives. This legislation controls the landing of ten orders of susceptible mammals ranging from elephants to primates. All imported animals are required to enter the country at designated seaports and airports. After landing they must be moved, by authorised carriers and in approved transportation, to registered quarantine premises (which is under the supervision of an official veterinarian), where they must remain for 6 months.

Special provisions based on risk have been made for some species. Vampire bats are placed in quarantine for life. This is because the vampire bat is one of the most important vectors of rabies to humans and mortality in the bats is low. Therefore, there is a risk that vampire bats may be persistently infected (McColl et al., 2000; Aguilar-Setien et al., 2005), however, no vampire bats have ever been imported into the UK.

Rodents and lagomorphs are exempt when they are destined to a facility licensed under the 'Animal Scientific Procedures Act' of 1986 or the 'Zoo Licensing Act' of 1981. Livestock species (bovines, ovines, caprines, swine) and horses are permitted to move between European Member States through the use of official health certification, which removes the need for quarantine. Elephants and animals of the order *Artiodactyla* (pigs, sheep, goats, cattle, camelids, hippopotamuses and others) imported from outside the EU must be kept at the place of destination for 30 days and may only be released by an authorised officer. These lesser requirements reflect the unlikelihood of these species transmitting rabies to humans or other animals.

These regulations were recently tested with the case of a consignment of young dogs being imported from Sri Lanka. In April 2008, a group of five stray dogs were being housed under current quarantine regulations at a quarantine centre in North East London. Nine days after arriving at the centre, one of the five dogs died and tested strongly positive for rabies antigen in a brain sample submitted to the Veterinary Laboratories Agency (VLA). This finding immediately led to a full public investigation trying to track all who may have come into contact with the infected animals, and arranging rabies post-exposure prophylaxis (PEP) where necessary. Vaccination status of those reported to have had contact with the puppy varied enormously with several individuals having had no pre-immunisation against the virus (Fooks et al., 2008).

This was the first case of rabies in quarantine in the UK for over 18 years. As this occurred inside a quarantine facility the 'rabies-free' status of the UK was unaffected. Variation in pre-exposure immunity among those involved in handling the infected animals highlighted the importance of ensuring that all persons who regularly handle imported animals receive complete rabies pre-exposure immunisation: generally three doses of rabies vaccine (on days 0, 7 and 28) followed by a booster at 1 year. During this incident, rapid laboratory diagnosis, close inter-agency working between Department for Environment, Food and Rural Affairs (Defra), the Department of Health (DoH) and the Health Protection Agency (HPA), and a prompt operational response at local level, permitted the timely identification of those who had at-risk contact with the rabid puppy and the initiation of appropriate PEP.

Quarantine requirements are still in force for all rabies susceptible animals other than domestic pet dogs, cats and ferrets that can enter the UK under the PETS regulations. It is important to note that if animals are proved to be non-compliant with the PETS regulations the animal will be required to enter quarantine for 6 months. Whilst the 6-month quarantine period is currently maintained, many commentators believe that 6 months is a disproportionate waiting period and that three months may be sufficient.

### 2.2. Animals leaving and re-entering the UK

The PETS travel scheme was initiated in the UK on 28th February 2000. This scheme served to allow fluidity of companion animal movement within qualifying countries for those that are able to fulfill various requirements regarding health and vaccination status. Initially only the 22 European Member States were able to use PETS enabling movement of animals into the UK although now several other countries qualify under the scheme, including Andorra, Gibraltar, Iceland, Liechtenstein, Luxembourg, Monaco, Norway, San Marino, Sweden and the Vatican.

Several requirements have to be met for animals to qualify for travel to and from the UK to these countries, including microchipping of pets, rabies vaccination and blood testing to assess suitable antibody titres within rabies vaccinated animals. On completion of these requirements owners are presented with a PETS certificate and are able to transport their animals out of, and back into, the UK. PETS certificates are valid for a period of six months after serological

**Table 1**  
Cases of EBLV-2 across Europe.

Year	Location	Virus reference	Bat specie	Reference
1985	Finland	RV8	Human	Lumio et al. (1986)
1987	Tjerkwerd, The Netherlands	RV29	<i>M. dasycneme</i>	Van der Poel et al. (2005)
1989	The Netherlands	RV228	<i>M. dasycneme</i>	Van der Poel et al. (2005)
1989	Switzerland	RV594	<i>M. daub.</i>	Lumio et al. (1986)
1989	Switzerland	RV621	Unknown sp.	Lumio et al. (1986)
1996	New Haven, Sussex	RV628	<i>M. daub.</i>	Whitby et al. (2000)
2002	Carnforth, Lancashire	RV1332	<i>M. daub.</i>	Johnson et al. (2003)
2002	Angus, Scotland	RV1333	Human	Fooks et al. (2003c)
2004	Staines, Surrey	RV1787	<i>M. daub.</i>	Fooks et al. (2004b)
2004	Blackburn Lancashire	RV1788	<i>M. daub.</i>	Fooks et al., 2004b
2006	Abingdon, Oxfordshire	RV2159	<i>M. daub.</i>	Fooks et al. (2006)
2007	Stokesay Castle, Shropshire	RV2336	<i>M. daub.</i>	Harris et al. (2007)
2007	Germany	n/a	<i>M. daub.</i>	Freuling et al. (2008)
2008	Teddington, Surrey	RV2418	<i>M. daub.</i>	Pajamo et al. (2008)
2008	Stokesay Castle, Shropshire	RV2473	<i>M. daub.</i>	Banyard et al. (2009)
2009	West Lothian, Scotland	RV2482	<i>M. daub.</i>	Horton et al. (2009)
2009	Finland	n/a	<i>M. daub.</i>	Jakava-Viljanen et al. (2010)

testing until the next date that a rabies booster vaccination is due. Furthermore, before allowing re-entry of certificated animals into the UK, owners are required to gain another certificate to show that their animals have been treated for tick and tapeworm infestation between 24 and 48 h before airport or seaport check-in. Owners are also required to sign a declaration that their animals have not been outside of any qualifying countries during the previous 6 months.

In 2001, a number of island nations that had 'rabies-free' status were included in the scheme, greatly increasing the number of holiday destinations that people could travel to, accompanied by their animals. While PETS has proved hugely successful in allowing certificated vaccinated animals to move between rabies-free areas, quarantine regulations are still enforced for importations from endemically infected areas.

### 2.3. Animal importation

There are extensive powers provided to enforcement agencies to ensure that the UK and the EU remain protected from rabies. Live animal imports from countries outside the EU must enter at a specified border inspection post and be examined by a veterinary officer. If these examinations reveal that an animal is likely to constitute a danger to animal or human health the animal may be seized and destroyed. Illegal consignments are placed in quarantine, or re-dispatched outside the territory of the European Community. Unintentional imports also occur with animal stowaways being discovered at seaports and airports. These animals should also be submitted to complete quarantine.

Currently, the UK imposes stricter rules on pet travel compared to most other European states. The UK and other EU member states (Finland, Ireland, Malta and Sweden), impose heightened requirements for animals to be assessed serologically to confirm rabies vaccination as well as be certified as having been treated for potential tick and tapeworm infestation prior to entry into the UK. This increased requirement may soon, however, be reduced as derogations in place to sustain these rules are due to expire in December 2011. Whilst it seems inevitable that the current derogation will end, the proposed alteration to current legislation needs to ensure that both public and animal health are safeguarded as we move towards the elimination of terrestrial rabies across the EU.

### 2.4. UK bats and rabies: the European bat lyssaviruses

The discovery of European bat lyssavirus (EBLV) type-2 in a Daubenton's bat (*Myotis daubentonii*) in 1996 in East Sussex fuelled concerns that bat rabies may be present within the UK and that there was a real threat of rabies entering the UK via migratory bats

(Whitby et al. 2000). Following numerous cases of lyssavirus positive bats across Europe it is now accepted that bat lyssaviruses are endemic within UK and European bat populations. Cases of lyssavirus infection of both bats and incidences of spill-over infection from bats into humans and terrestrial wildlife species continue to occur, albeit rarely, across Europe. The majority of cases of EBLV-1 have been reported in Serotine bats (*Eptesicus serotinus*) (Fooks et al., 2003a), although a number of other species are susceptible to infection (Vazquez-Moron et al., 2008; Muller et al., 2007). Furthermore, EBLV-1 infection has also been reported in spill-over events, in incidental hosts including a stone marten, sheep and humans (Muller et al., 2004; Ronsholt, 2002; Selimov et al., 1989) with seropositivity and antigen detection in domestic cats also being reported (Dacheux et al., 2009; Bourhy et al., 2005; Tjornehoj et al., 2004). In comparison to EBLV-1, EBLV-2 has been reported on fewer occasions, having been detected in both Daubenton's bats (*Myotis daubentonii*), native to the UK and pond bats (*Myotis dasycneme*), a European species occasionally found in the UK. As well as having been isolated in the UK, EBLV-2 isolates have also been reported in Switzerland, Holland, Germany and Finland (Lumio et al., 1986; Van der Poel et al., 2005; Muller et al., 2007; Freuling et al., 2008; Jakava-Viljanen et al., 2010).

Since 1996, EBLV-2 has been detected in several locations across the UK suggesting that EBLV-2 is endemic at a low level in British bats. Most recently, live EBLV-2 virus was isolated from a Daubenton's bat in Scotland (Horton et al., 2009) (Table 1). As a result of EBLV isolation from UK bats, the VLA undertakes passive surveillance on all bats submitted to regional and national laboratories. Bat groups, such as the Bat Conservation Trust as well as other bat enthusiast groups, and members of the public are requested to be aware of, report and submit for testing any grounded bats, bats found dead or those acting unusually. Whilst a number of different infectious agents are known to infect bats, testing for lyssaviruses is of paramount importance due to the potential impact on human health.

Both passive and active surveillance strategies have been implemented and annually large numbers of bats are submitted for testing (Harris et al., 2006). Passive surveillance testing of UK bats started in 1987 and since then, up to and including 2009, a total of 10,340 bats have been submitted for testing for lyssavirus infection. This initiative has enabled detection of nine lyssavirus antigen-positive bats as well as identification of roosts, which required further investigation to assess seroprevalence. Of this total, a small percentage were Daubenton's bats (2.7%), the suggested primary host for EBLV-2 and even fewer were Serotine bats (1.2%), the suggested host for EBLV-1 (Fig. 1). The majority of bats submitted for testing are Common Pipistrelle bats (72.5%), although to date there

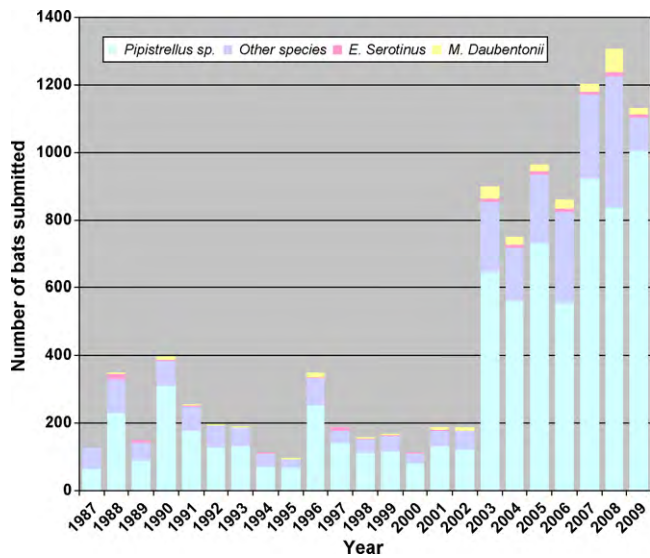


Fig. 1. Number and species of bats submitted for rabies virus testing at the VLA (1987–2009). Bat species of interest are colour coded as per the key.

has been no indication of EBLV infection in *Pipistrelle* species in the UK.

The recent development of genetic speciation for UK bats based on cytochrome B sequence has improved surveillance strategies although, passive surveillance, will by its nature, generate a bias towards testing certain (more susceptible) species of bat (Harris et al., 2009). In particular, the species of bats most often received are generally a factor of geographical location of roosts and the resulting proximity to humans and their pets. As many as 17% of submitted bats were brought into human habitation by pet cats (Harris et al., 2009). Obviously, bats that establish roost sites in buildings that are frequented by members of the public are more likely to be noticed, collected, and submitted when they are found dead or injured, a factor that has led to the repeated detection of EBLV-2 from a single location over a 2-year period (Banyard et al., 2009).

As well as passive surveillance of bat populations, active surveillance initiatives have also been undertaken. Between 2003 and 2006, the VLA, in collaboration with Scottish Executive, Scottish Natural Heritage, and Defra undertook targeted surveillance for European bat lyssaviruses throughout Scotland and England, focussing on the two bat species most likely to host these viruses, Daubenton's and Serotine bats (Harris et al., 2009). Blood and oropharyngeal swabs were taken for the detection of EBLV-specific neutralising antibodies and viral RNA or infectious virus in saliva, respectively. This initiative sampled 273 Serotine bats and 363 Daubenton's bats with the conclusion that, in the populations tested, there was an EBLV-2 antibody prevalence of 1.0–4.1% (95% CI, mean = 2.2%). Interestingly, EBLV-1-specific antibodies were only detected from one sample in a Serotine bat. The seroprevalence of EBLV-2 within Daubenton's bats reported in this study is very low compared to data from Spanish bat populations where much greater seroconversion levels were reported (Perez-Jorda et al., 1995; Vazquez-Moron et al., 2008; Serra Cobo et al., 2002). This study proved that EBLV-2 infection is maintained in Daubenton's bat populations in the UK. The detection of only a single Serotine bat with EBLV-1-specific antibodies suggests that it is unlikely that EBLV-1 circulates in this species in England (Harris et al., 2009). Interestingly, between 1987 and 2009, 129 Serotine bats were examined through the passive surveillance scheme and all were negative for lyssavirus infection by fluorescent antibody test (FAT). From a geographical point of view, the UK population of Serotine

bats seems to be restricted to southern England, often roosting in residential properties. The species is one of the least common in the UK with an estimated population of less than 15,000 individuals. With transmission of virus often linked to the availability of new vectors, it is thought that low numbers of Serotine bats in the UK may preclude maintenance of EBLV-1 in UK roosts (Harris et al., 2009).

The threat to the UK population posed by these viruses remains low. It is essentially unknown whether or not EBLV-1 will enter the UK bat population in future and increase this threat. Furthermore, maintenance of these viruses within bat populations is very poorly understood, as is the case for all other lyssavirus infections in bats, and a greater understanding of bat populations and ecology is required to answer questions that remain. Also, the apparent restricted infection of certain bat species in the UK and Europe is not understood. It is known that in the UK, Daubenton's bats co-roost with other species yet EBLV-2 infection of other UK bats has not been detected. The threat of EBLV-2 spill-over into the human population remains, however, and with one human death attributed to infection with this virus, the risk is not to be ignored.

## 2.5. Rabies and travel

Generally the threat of rabies virus infection to travelers from the UK is low. However, for individuals who choose to travel to rabies endemic areas the risk is increased and in recent years there have been several tragic cases of individuals being exposed to rabies virus abroad. Where PEP was not administered, human deaths have occurred upon return to the UK. Incubation periods following exposure are variable and whilst often clinical disease ensues soon after infection, in some instances the incubation period can be considerably longer. The recent case of a 37-year-old woman from Northern Ireland dying from rabies virus infection following an incubation period of what may be up to 2 years illustrates this point. In this instance, the individual in question did not seek medical attention following an incident with aggressive dogs in South Africa (Hunter et al., 2010). Human rabies cases in the UK where exposure occurred abroad over the last 10 years are detailed in Table 2. A similar situation exists across Europe. The recent death of a Dutch traveler from infection with Duvenhage virus, a virus closely related to rabies virus, further illustrates the potential danger of these viruses to travelers. Here, a bat had flown into the face of a 34-year-old woman and very small puncture marks were identified on her face. Whilst the wound was washed with both detergent and alcohol swabs, PEP was not administered and 23 days after coming into contact with the bat, symptoms of clinical disease started to develop (van Thiel et al., 2008).

A recent study in France evaluated cases of international travelers exposed to potentially rabid animals. The study highlights the fact that the majority of cases were reported from North Africa (41.5%) and Asia (22.2%) and a lack of awareness when seeking medical advice regarding vaccinations. Indeed in those countries where at-risk injuries were recorded (Algeria, Morocco, Tunisia, Thailand, and Turkey), travelers do not usually seek advice from specialized travel clinics, as the areas involved are not at risk for specific travel-associated diseases like malaria or yellow fever. Interestingly, a correlation between the likelihood of being bitten by a certain animal species was made, with dogs being more frequently involved in Algeria, cats in Tunisia and the Middle East, and non-human primates in sub-Saharan Africa, Madagascar, and Asia (Gautret et al., 2010).

For UK citizens, pre-immunisation is recommended for travel to certain areas although not all travelers follow the recommended course of vaccination. The cost of vaccinations, as well as lack of information sought with respect to the potential threat from rabies, often precludes administration of vaccine. However, the

**Table 2**  
Human genotype 1 rabies cases imported by travelers to the UK over the last 10 years.

Year	Nationality	Sex	Age	Source	Bite site	Incubation period	PEP administered?	Reference
2001	Phillipino	M	55	Philippines	Dog bite (hand)	~1.5 months	No	Smith et al. (2003)
2001	Nigerian	F	52	Nigeria	Dog bite (leg)	~5 months	Medical advice sought and injections given although unclear if this was rabies vaccine	Johnson et al. (2002, 2005)
2005	British	F	37	India (Goa)	Dog bite (Left leg)	~3 months	No	Solomon et al. (2005)
2009	British	F	37	South Africa (KZN)	Dog bite	Up to 24 months	No	Hunter et al. (2010)

importance of pre-immunization cannot be ignored. Furthermore, in cases where exposure to the virus is suspected, whether by bites, scratches or other means of exposure, individuals should seek medical advice without delay. This also applies to travelers in low risk areas as other infectious agents may be present, or the animal may have strayed from an area of endemicity. Indeed, even if the traveler exposed has been vaccinated, medical advice should be sought without delay. In addition to recommendations to seek medical advice, a few sensible precautions can be taken to avoid exposure in the first place. Contact with all wild or domestic animals should be avoided during travel. Simple first aid measures should also be taken if exposure is suspected. Washing the wound, if an animal bite has occurred, or site of exposure in the case of scratches or exchange of saliva to mucous membranes, with detergent for at least 5 min is strongly advised. If possible the area exposed to potential infection should also be doused in either iodine solution or, as iodine is often unavailable, a 40–50% alcohol solution where possible. These simple measures can greatly influence the outcome of exposure (Fooks et al., 2003b).

### 3. Concluding remarks

The implementation of strict legislation and quarantine in the UK has enabled the maintenance of a 'rabies-free' status and has ensured rapid containment of rabies infected animals that have entered the country. Furthermore, a complex framework exists that supports a strong contingency plan should the virus enter the country. However, there is no doubt that the risk of introduction into the UK of rabies and other exotic diseases remains. Across Europe a number of other human pathogens have been shown to be emerging that may, in the future, pose a greater risk to the UK population. Two cases of Lassa fever in travelers returning to the UK from Nigeria and Mali in February 2009 show a potential threat to the UK population. Whilst rare, Lassa fever is able to be transmitted between humans, and therefore, exposed individuals could be at risk (Atkin et al., 2009; Kitching et al., 2009). Health surveillance for individuals having had contact was necessary to ensure freedom from further disease.

Indeed, the development of sensitive molecular tools and increased surveillance of wildlife populations has highlighted a number of pathogens with zoonotic potential that pose a threat to human populations. The international travel of both humans and animals increases the risk of interaction with species harboring zoonotic disease and also the risk of global spread of disease in infected individuals that are unaware they have even been exposed. Recent 'explosions' of zoonotic pathogens highlight the continued risk to populations to emerging diseases. SARS coronavirus, pandemic and avian influenza virus, West Nile Fever virus and to a lesser extent Crimean Congo Hemorrhagic Fever virus have, in recent years, increased our awareness of the threat from zoonotic pathogens.

The control measures that have proved so effective in preventing rabies incursion need to be constantly reviewed and modified to ensure that they mitigate against potential exposure pathways. Routes of introduction are continually affected by increasing inter-

national travel and trade, movement of potential reservoir species and urbanization of wildlife. Novel control measures in response to new and emerging diseases will need to be considered in order to respond proportionately and effectively.

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