Rabies in North America and Europe

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Rabies is caused by infection with a negative-stranded RNA virus within the *Lyssavirus* genus (family Rhabdoviridae, order Mononegavirales), mainly transmitted via saliva following a bite from an infected animal. Transmission may also occur through mucous membranes, but not through intact skin. The main source of infection from domestic reservoir species is dogs and cats.

There are seven rabies virus (RV) genotypes, six of which have similar effects in man; the exception is genotype 2, which has never been isolated in human cases. The main genotypes of interest for the purpose of this review are 1, 5 and 6. Genotype 1 viruses have a worldwide distribution and are generally found in terrestrial animals. Genotypes 5 and 6, commonly known as European bat lyssaviruses (EBLs), are restricted in distribution to Europe and are frequently isolated from European bats. Genotype 1 viruses have never been isolated from European bats.

Rabies can probably infect most if not all mammals. The virus enters the central nervous system of the new host, causing an encephalomyelitis which is always fatal once symptoms develop. The manifestations in human cases include spasms, hallucinations, hydrophobia, aerophobia, dysphasia, paralysis and coma. Extreme agitation and convulsions can be interspersed with periods of lucidity. World wide, the disease causes many thousands of human deaths each year. The World Health Organization (WHO) World Survey of Rabies for the year 1997 gave an estimate of between 35 000 and 50 000 annually[1]. Gross under-reporting is likely because many countries lack the necessary diagnostic facilities; also, the populations most affected tend to be rural (especially in developing countries) with erratic notification systems. African and Asian countries are particularly affected because of their animal reservoirs and the lack of healthcare and control measures. The subject has been thoroughly reviewed by King and Turner[2]. Here we focus on human rabies in North America and Europe.

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HUMAN RABIES

North America

Until recently it was difficult to identify which strains of RV were causing human disease. This has changed with the advent of molecular diagnostic tools such as nucleotide analysis, which also provide clues to the source of the virus. It now seems that a large proportion of human rabies infections in the United States are transmitted by bat bites. Some people when bitten ignore the danger and take no action; many are simply unaware of the bite—perhaps because they are asleep when it happened. Also, parents may not know that their children have been in contact with bats.

Since the 1900s, the number of deaths from rabies in North America has fallen from 100 or more each year to just one or two cases. Much of the decline dates from the 1940s, when vaccination and animal control programmes were set up. In the early 1940s, there were about 40 cases each year[3]. This figure decreased to a total of 99 for the entire decade in the 1950s, and then dropped further to 15 in the 1960s, 23 in the 1970s, 10 in the 1980s and 22 from 1990 to 1996[4]. Widespread vaccination of canine pets in the 1950s was partly responsible for the decrease in human cases in subsequent years[5]. The vaccination campaigns implemented in the 1940s all but eliminated the circulation of canine strains of genotype 1 RV by the 1960s. However, the late 1970s and early 1980s witnessed the re-emergence of a variant well adapted to dogs in south Texas[6], thereby increasing the risk to human beings.

4 human cases were reported in 1997 (Montana, Washington, Texas and New Jersey) and just 1 case in 1998 (Virginia). No human deaths were recorded in the USA for 1999 but in 2000 there were 5, reported from California, New York, Georgia, Minnesota and Wisconsin plus 1 from Quebec (Canada)[7]. The case reported from New York was in a patient who had come from Ghana after being bitten by a dog; all the others were thought to be associated with bats.

Europe

Human cases in Europe have been well documented since the late 1970s. In 1997 17 human cases were reported[8]—12 from the Russian Federation, 3 from Romania, 1 from Lithuania and 1 from France (imported). In 1998 the total

was 7 cases and in 1999 it was 11 (all reported by the Russian Federation)[8]. In 2000 the total was 9—7 reported by the Russian Federation, 1 by Romania and 1 by Lithuania[8].

In June 2001 the UK had 2 human cases—the first being imported from the Philippines and the second from Nigeria. Both were confirmed in our laboratory as genotype 1 canine strains by virus sequence analysis. The previous introductions of rabies into the UK were both in 1996. There was an imported human case from Nigeria (genotype 1) and a Daubenton's bat case (EBL 2, genotype 6, which may have originated from mainland Europe[9]). The bat had bitten 2 people, both of whom successfully completed post-exposure prophylaxis (PEP). Because the human cases had been imported and the bat was harbouring a EBL, the rabies-free status of the UK remained unaffected.

RABIES VACCINES FOR HUMAN USE

Pre-exposure

Safe and potent rabies vaccines are available for use in man. Both pre-exposure and post-exposure treatments for rabies have been harmonized across Europe and North America following the guidelines set by the WHO. The vaccine currently employed in the UK is a rabies human diploid cell vaccine (HDCV). Easily accessible, it is a freeze-dried suspension of Wistar RV strain PM/WI 38 1503-3M. Pre-exposure prophylaxis is routinely offered to those whose occupation may lead to exposure to rabies viruses. These include workers at animal quarantine centres, at zoos, at research and acclimatization centres where non-human primates and other imported animals are housed, and certain customs and excise officers, veterinary and technical staff in the State Veterinary Services, inspectors appointed by local authorities under the Animal Health Act 1981, bat handlers and laboratory workers[1]. The recommended schedule for primary pre-exposure immunization with HDCV is three doses given by deep subcutaneous or intramuscular injection in the deltoid region on days 0, 7 and 28. The antibody response may be lower with gluteal injection. Travellers to rabies endemic areas are offered two doses by deep subcutaneous or intramuscular injection four weeks apart, and this can be expected to give immunity in 98% of recipients. This level of protection may be acceptable if post-exposure treatment is likely to be readily available. However, for those travellers with continued exposure to rabies viruses a further dose should be given 6–12 months later[1].

Post-exposure

The treatment regimen after exposure depends on several factors. Daily doses of vaccine in the abdomen are no longer necessary. The strategy recommended by WHO is essentially as follows. Patients who have had a pre-exposure course of HDCV should be given two subcutaneous or intramuscular doses of HDCV in the deltoid region, one on day 0 and one between days 3 and 7. For children, vaccine can be delivered in the anterolateral aspect of the thigh[1].

Previously unimmunized individuals should be given, in addition to vaccine, rabies immunoglobulin in a dose of 20 IU/kg body weight. Up to half the dose should be infiltrated in and around the wound after cleansing and the rest by intramuscular injection. HDCV should be delivered by subcutaneous or intramuscular injection (not the buttocks), on days 0, 3, 7, 14, and 30[1].

WILD AND DOMESTIC ANIMALS

North America

Since the 1950s raccoons have continued to be an important reservoir for the circulation of rabies in the south-eastern States of North America. In addition, three strains of RV seem to cause disease in skunks in the north and south central States and in California[9]. The disease spread in the 1950s, affecting foxes across Canada and in New England. Although rabid foxes have declined in Canada as a result of successful baiting strategies, Alaska still harbours the virus in the red and arctic fox populations[6].

In the United States over the past 40 years, most of the reports of rabies have been in wild rather than domestic animals. During 1998, wild animals accounted for 92.4% of all cases reported to the Centers for Disease Control and Prevention[6]. Raccoons are the species reported most frequently to harbour the disease (40.6%), followed by skunks and bats (29.4% and 14% respectively). Foxes accounted for 5.4%[10]. Outbreaks of rabies infections in terrestrial mammals inclusive of skunks, foxes, raccoons and coyotes are found in broad geographic regions across the US[10]. Hawaii is a unique State in that it has never reported an indigenously acquired human or animal case of rabies[10].

Interestingly, from 1998 to 1999, cases of rabies in feline, canine and equine species decreased by 1.4%, 1.8% and 20.7%, respectively, whereas those in bovine, ovine and porcine species increased by 16.4%, 12.5% and 200.0%. The two States reporting the highest number of rabid domestic animals were Iowa (57) and Texas (54)[10]. For the first time, a bat-associated RV was isolated from a cat—in Maryland[11].

In North America, bat rabies is caused by genotype 1 viruses. The main species involved are *Eptesicus fuscus*, the big brown bat; *Tadarida brasiliensis*, the Brazilian (Mexican) free-tailed bat; *Myotis lucifugus*, the little brown bat; *Lasiurus cinereus*, the hoary bat; *Lasionycteris noctivagans*, the

silver-haired bat, *L. borealis*, the red bat; and *Pipistrellus hesperus*, the western pipistrelle.

Control

Although human rabies cases are rare in the US, as many as 16 000–39 000 people receive PEP every year[12]. The persistence of RV in a broad range of native species continues to present a public health hazard.

Controlling rabies in the US is a complex issue. In contrast to Europe, for a given area the principal vectors for the disease are multiple rather than a single wildlife species. Vaccination of domestic pets, observation of suspect animals and public education have all assisted in controlling rabies in domestic animals. However, these activities are not sufficient to eliminate sylvatic rabies.

Population reduction techniques have been employed in the past in an attempt to reduce susceptible animals below the threshold necessary for rabies to spread through populations[13]. The programme to control skunks infected with rabies in Alberta, Canada, is a prime example of this method[14].

Modifications to habitats are simple ways in which human/animal contact is minimized. Routine rubbish disposal and pick-up (with animal-proof receptacles, capping chimneys and screening vents) can help to achieve this objective. All these methods minimize human/animal contact and so reduce the need for PEP, which is costly and can generate much anxiety.

Trap–vaccinate–release (TVR) programmes have also been employed with success. Such a programme was tested in Toronto in 1984 in an effort to control skunk rabies before an oral rabies vaccine (ORV) had been developed. The scheme cost in the region of $450–$1150 per km^2. However, some of these costs were offset by fewer people needing PEP[15].

Between July and October 1999, an emergency response was implemented to combat rabies in Ontario. The objective was to contain the first three confirmed cases of raccoon rabies in Canada. The strategy employed was known as point infection control and involved the combination of TVR, ORV and population reduction[16]. Oral rabies vaccination was implemented in Ontario by the Ministry of Natural Resources from 26 to 28 June 2000, with a planned drop of 300 000 baits containing vaccine against the raccoon strain of RV. The target area stretched from Napanee to Cornwall. To maximize safety and exposure, baits were placed by hand in urban areas.

Currently, field trials are underway in specific States in the USA with a vaccinia recombinant expressing the RV glycoprotein (VRG). In September 2000, a 28-year-old pregnant woman was bitten by her pet dog whilst attempting to remove a VRG bait from the dog's mouth. Material from the woman's wound was cultured *in vitro* and demonstrated a virus with a poxvirus morphology[17]. Although an isolated case, this incident may create difficulties for VRG use near urban areas and emphasizes the need to prevent accidental human exposure when using VRG.

Europe

8155 cases of animal rabies were reported in Europe in 2000[18]. Wild animals accounted for 72.1%. Of the domestic animals, dogs (34.2%) and cats (26.1%) ranked highest as hosts to RV. Foxes (83.4%) and raccoon dogs (*Nyctereutes procyonoides*) (10.5%) represented most of the wild animal hosts for classic rabies.

Rabies in Europe provides excellent examples of temporal change in the reservoir species and geographical spread. The reduction of wolves (*Canis lupus*) and stray animals diminished two ancestral reservoirs for rabies during the 1900s[16], leaving central Europe rabies-free for many years. It was soon clear, however, that rabies had not been eliminated since new reservoir species emerged[19]. There are reports of RV being isolated from wild rodents in many countries, including the Russian Federation and Germany[20]. However, there is no evidence of virus adaptation in rodents to date. The epizootic of rabies in the red fox started in 1939–1940 on the Russian–Polish border and in northern Poland[21–23]. After a period of adaptation, the disease spread in foxes to the rest of Europe, moving south and west at 20–60 km/year. The progression of disease was well documented from 1945[24], reaching France by 1968[23,25] and Northern Italy in the early 1980s[26,27].

The main reservoir host species of classic RV in Europe remains the red fox and the raccoon dog. Raccoon dogs were introduced into western Russia for fur farming in the 1920s; they subsequently spread throughout much of Eastern Europe and north to Finland. The arrival of the omnivorous raccoon dog further complicates the control of red fox rabies in Eastern Europe. There is evidence that, during their winter hibernation, raccoon dogs can incubate RV and so cause the disease to persist from one season to the next in geographical areas where fox densities are so low that rabies might otherwise die out[28].

EBLs are common in insectivorous bats throughout parts of Europe and hence are important reservoirs of sylvatic rabies. The importance of bat rabies (specifically EBLs) as a 'spill-over' threat to humans and terrestrial animals, domestic and wild (including badgers and rodents), remains unclear. From 1977 to 2000, 630 cases of bat rabies were reported in Europe, 3 of which were human cases[8].

In Europe, bat rabies isolates are genetically different from those found in bats in North America. The species involved are *Eptesicus serotinus*, the principal reservoir for

genotype 5, *Myotis dasycneme* and *M. daubentonii*, the principal reservoirs for genotype 6. To date, there is no evidence that spill-over infections to other mammals have resulted in host adaptation.

Of the domestic animal species in Europe, ruminants, dogs (*Canis familiaris*), and cats remain important hosts for classic rabies. Rabies in companion animals within Europe has been largely controlled (except in Turkey and the Russian Federation) and is being successfully reduced in foxes by vaccination programmes[29].

Control

Countries that have not reported any cases of indigenous rabies in mammals (excluding EBLs) for at least two years are recognized by the Office International des Epizooties (OIE) as rabies-free. In addition, countries must practise active surveillance strategies and have statutory importation policies in place for rabies.

Historically, the destruction of foxes failed to reduce the spread of the epizootic. More recently, many of the successful control measures undertaken to combat fox rabies in Europe have employed oral vaccines. The rabies vaccines for oral immunization are based on the Street Alabama Dufferin (SAD) strain of rabies virus or VRG. Switzerland hosted the first field trial with the attenuated strain SAD Berne in 1978[30]. In 1986, some European countries employed SAD B19. In 1991, SAG 1, a mutated version of SAD Berne was employed and this has since been superseded by a more genetically stable vaccine, SAG 2. However, there was and still is concern over safety and stability when using attenuated strains. In the hope of allaying this safety concern VRG was developed and tested in the field for oral vaccination of foxes[31]. Since 1989, the increased use of VRG has been instrumental in successfully eliminating sylvatic rabies from large areas within Europe. However, following the success of the vaccination campaigns, complacency may result in a partial or total halt to control programmes and thus allow the reintroduction of rabies from endemic areas into rabies-free areas. There is also the threat that genotypes now found in bats may adapt to other species of mammals. An EBL has been detected in three sheep in Denmark[32]; hence, there is a risk that EBL may adapt to terrestrial mammals. Adaptation to carnivorous mammals would obviously pose the greatest risk. Fox rabies control measures are ineffective against bats and may not be effective against raccoon dogs. This is because different baits are often necessary for enticing different mammals to take up the vaccine-containing materials.

The UK Government aims to keep rabies out of the country by employing stringent quarantine and import controls. Controls include compulsory quarantine for six months unless the animals are exempt under the 'Balai Directive' (set up for commercial trading of cats and dogs), or the Pet Travel Scheme (PETS). In February 2000, a pilot Pet Travel Scheme was introduced that allows for the free movement of domestic dogs and cats to the UK from specific countries in Europe without quarantine. The full scheme was launched in April 2001. To qualify, each animal is required to be fitted with a microchip (tattoos are not accepted). In addition, it must be vaccinated against rabies with inactivated vaccine and shown to have developed RV neutralizing antibodies by a recognized laboratory. Furthermore, all pet owners have to testify that the animal has not been outside of the qualifying countries in the six months before travel. The animal is then issued with a travel certificate. Pets may not enter the UK under PETS until six months from the date that a veterinary surgeon took the blood sample that led to a successful test result. Before re-entering the country the animal must also be treated against ticks and tapeworms.

The Government is considering whether the scheme should be extended to include North America even though in parts of that continent rabies is endemic in wildlife.

CONCLUSIONS

In some areas of the US, the control of sylvatic rabies remains problematic. In Europe, control programmes have been largely successful. The list of countries now classified as rabies-free is expanding, one of the more recent additions being France.

Rabies infections of terrestrial animals tend to appear in discrete areas and transmission occurs mainly between members of the same species. In Europe and the US it is highly unusual to find bat-associated variants of rabies in other mammals (except when human exposure has occurred). There is concern in the US over the colonies of different bat species that live in and around dwellings inhabited by man. Just as the EBLs are not known to have adapted to mammals in Europe, some bat variants of genotype 1 exist in the US that seem to be maintained only within unique bat species. Similarly, the Australian bat lyssavirus appears to be maintained only within indigenous bat populations[33]. The reported isolation of a EBL1 in sheep in Denmark raises concerns that lyssavirus adaptation to new hosts may occur. This would be especially worrying should densities of a new host be high enough to allow rapid dissemination of an adapted virus. Surveillance must continue. In addition, experiments to determine the risk of EBL transmission to terrestrial wild and domestic animals are underway in several European laboratories.

Perhaps the biggest concern is the continual threat that rabies may be reintroduced from a rabies-infected area into a rabies-free zone as a result of complacency, political

instability or lack of funding for control campaigns. To minimize human contact with rabies, the disease must be controlled in animals.

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