Eradicating rabies at source

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Summary

Along with zoonotic influenza and antimicrobial resistance, rabies has been identified as a key One Health issue by the World Organisation for Animal Health (OIE), World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO). It provides an excellent example of a disease that has an impact on public, animal and environmental health, and therefore benefits from a One Health approach to management. Regrettably, this zoonotic disease is still neglected despite the fact that, annually, it kills as many as 70,000 people worldwide (chiefly children in Asia and Africa), millions of dogs suffer and die, and the disease threatens some populations of endangered wildlife. This is particularly unfortunate, given that effective means of prevention exist. As Her Royal Highness Princess Haya of Jordan pointed out in a video to mark World Rabies Day on 28 September 2013, rabies is a serious world public health problem that is all too often underestimated and even neglected. Yet we know it can be eliminated. By combatting rabies at its source in animals and vaccinating 70% of dogs, we can eradicate it.

Keywords

Epidemiology – Eradication – Lyssavirus – One Health – Rabies – Recombinant vaccinia-rabies virus – Stray dog – Vampire bat – Wildlife.

Introduction

Along with zoonotic influenza and antimicrobial resistance, rabies has been identified as a key One Health issue by the World Organisation for Animal Health (OIE), World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO). It provides an excellent example of a disease that affects public, animal and environmental health, and which therefore benefits from a One Health approach to management. Regrettably, this zoonotic disease is still neglected, even though annually it kills as many as 70,000 people worldwide, chiefly in Asia and Africa. Most rabies victims are children who have been bitten by a dog. After the onset of symptoms, rabies is always fatal and causes extreme suffering before death. Rabies also causes suffering and mortality in dogs themselves, and threatens some populations of endangered or threatened wildlife species. This is all the more unfortunate, given that highly effective means of prevention (vaccines) exist. Traditionally, the main reason for controlling rabies is concern for public health, but the results of intervention in humans is unpredictable. Only a few risk groups benefit from preventive vaccination. In most cases, vaccination (with or without serum therapy) is used curatively following exposure. Therefore, the best solution is to combat the rabies infection at its source in animals. This has the advantage not only of preventing transmission to humans but also of enhancing animal and environmental health. As Her Royal Highness Princess Haya of Jordan pointed out in a video to mark World Rabies Day on 28 September 2013 (available on the OIE YouTube channel), rabies is a serious world public health problem that is all too often underestimated and even neglected. Yet we know it can be eliminated. By combatting rabies at its source in animals and vaccinating 70% of dogs, we can eradicate it.

Lyssaviruses

Rabies is caused by a negative-sense single-stranded ribonucleic acid (ssRNA) virus of the genus *Lyssavirus*, belonging to the family *Rhabdoviridae* of the order *Mononegavirales* (1, 2). According to the International Committee on Taxonomy of Viruses, the genus Lyssavirus is delineated into different viral species based on demarcation criteria (such as genetic distance and antigenic patterns in reactions with panels of anti-nucleocapsid monoclonal antibodies or polyclonal sera) and ecological criteria (such as geographic distribution and host range).

Lyssavirus species are divided into phylogroups. Phylogroup 1 includes: rabies virus; Duvenhage virus; European bat lyssavirus types 1 and 2; Australian bat lyssavirus; Aravan virus; Khujand virus and Irkut virus (3). Phylogroup 2 includes: Lagos bat virus; Mokola virus and Shimoni bat virus (4). As the West Caucasian bat virus does not cross-react serologically with any members of phylogroups 1 and 2, it is presumed to form part of a separate phylogroup (phylogroup 3) (3). The new viruses described in Eurasia are all associated with insectivorous bats and the Irkut virus has caused one human death. In 2010, a new lyssavirus was isolated in a Natterer's bat (*Myotis nattereri*) in Germany and was named Bokeloh bat lyssavirus (5). In May 2009, an African civet (*Civettictis civetta*) suspected of rabies was killed in Serengeti National Park (Tanzania). The virus isolated in this case was named Ikoma lyssavirus and it is genetically different from all previously known lyssaviruses, although it is distantly related to the West Caucasian bat virus (6).

The rabies virus is divided into different 'biotypes' corresponding to particular species, as shown by the epidemiology of rabies in the United States and Canada (7). In the 1950s, canine rabies was still endemic in the United States but control measures and parenteral vaccination brought it under control. In the United States and Canada, rabies reservoirs are now confined to wildlife, with different epidemiological cycles in different species. They include: raccoon (*Procyon lotor*); skunk (*Mephitis mephitis*); red fox (*Vulpes vulpes*); arctic fox (*Alopex lagopus*); coyote (*Canis latrans*) and insectivorous bats, of which the main species involved is the eastern pipistrelle (*Pipistrellus subflavus*). Although, in most cases, the distribution of different strains associated with particular species is geographically defined, some strains have been known to cross from one species to another (spillover). For example, insectivorous bat lyssaviruses have been isolated from cattle and foxes in Canada (8). Similarly, in Western Europe, strains have crossed the species barrier from insectivorous bats to terrestrial animals such as sheep (*Ovis aries*) (9, 10), beech martens (*Martes foina*) (11, 12) and cats (13). Some also believe that bat lyssaviruses are the ancestors of lyssaviruses.

Epidemiology of rabies

Terrestrial carnivores are the main reservoirs/vectors of rabies (terrestrial rabies). These reservoirs/vectors vary in terms of their geographical range. They include the skunk, mongoose, raccoon, fox, wolf, jackal, raccoon dog (*Nyctereutes procyonoides*) and, of course, the dog, especially stray (feral) dogs. These animals transmit the infection to other domestic or wild mammals, and to humans, usually through a bite with infected saliva. As mentioned earlier, the virus strains involved are distinct variants (biotypes), each of which is linked to a different reservoir/vector. In developing countries, the primary source of transmission to humans is the dog. Rabies kills an estimated 70,000 people annually worldwide, posing a very serious public, animal and environmental health problem. Even though solutions exist for eradicating canine rabies, proper measures are not applied everywhere. More often than not, the will and means for applying them are lacking. As mentioned earlier, bat lyssaviruses have been isolated in many species of insectivorous, fruit-eating and haematophagous bat throughout the world. A total of 1,116 bat species have been identified worldwide, and these species represent 20.6% of all currently known mammal species (14). Insectivorous bats are present in virtually every region of the globe. The species involved in lyssavirus transmission belong mainly to eight genera: *Eptesicus, Myotis, Lasiurus, Lasionycteris, Pipistrellus, Tadarida, Miniopterus* and *Nycteris* (8). Bats can spread the infection to terrestrial mammals, including humans. Furthermore, phylogenetic analyses suggest that host transfers can occasionally occur between a bat vector and a terrestrial carnivore, so enlarging the range of virus hosts. Bats are therefore an accidental yet continual and uncontrollable threat. A special case is the haematophagous bat, or common vampire bat (*Desmodus rotundus*) (15).

Rabies of haematophagous bats (vampire bats)

The common vampire bat is a non-migratory species living in colonies of up to several hundred individuals. While their preferred prey is cattle, they may also feed on humans. The first scientific evidence of the role of vampire bats in rabies transmission was provided in the first half of the 20th Century on the island of Trinidad (Trinidad and Tobago) and in Latin America (16, 17). In a country like Mexico, where rabies transmitted by stray dogs coexists with rabies transmitted by vampire bats, humans are regularly infected. A relatively simple technique (restriction pattern) can be used to determine the source of human infections (18). Vampire bats can excrete the rabies virus asymptomatically (19), but they eventually die from the disease.

In 1526, Gonzalo Fernández de Oviedo published *Sumario de la Natural Historia de Las Indias* to inform Emperor Charles V about the flora and fauna of Latin America (20). His work contains a description of haematophagous bats, which he referred to as vampire bats, capable of inflicting bites on humans and so transmitting a terrifying disease (probably rabies). The introduction of domestic livestock by the Spanish conquistadors had a significant impact on the ecology of local populations of common vampire bats. This massive influx of a new food source allowed common vampire bats to proliferate and expand their range. Vampire bat bites still pose a public and animal health hazard to this day. In countries where the vampire bat is rife, it and the dog are the main rabies reservoirs/vectors. Cattle are the foremost victims and bovine paralytic rabies has a significant economic impact. In 1991, Flores Crespo reported (21) that the vampire bat was still responsible for the death of 10,000 cattle per year in Mexico in the states colonised by vampire bats. He also signalled an alarming new development in several Latin American countries: an increasing number of bat bites inflicted on humans. In Mexico, for example, vampire bats are the second most important vector of human rabies after dogs. Research on the biology of vampire bats found that rabies transmitted by vampire bats could be controlled either by reducing populations of the vector species or by rabies vaccination of cattle. The application of these control measures has reduced the incidence of rabies in domestic livestock (22). Methods for destroying vampire bats are based mainly on the use of anticoagulants. Two behavioural characteristics of vampire bats have been exploited to poison them by the oral route with anticoagulants: their feeding behaviour and personal or mutual grooming behaviour. One method is to capture a few subjects from a colony and coat them with anticoagulant before releasing them back into the colony. The other colony members become poisoned by licking the treated animals. A single treated subject can poison between 10 and 40 colony members. Anticoagulants can also be applied to wounds on domestic animals, as vampire bats show a preference for existing wounds. Another method is to administer anticoagulants to cattle themselves at a dose harmless to them but lethal to vampire bats (23). Experimental vaccination trials have also been conducted on vampire bats (24), in particular using the recombinant vaccinia-rabies vaccine, but this method is virtually unworkable in the field (25).

The impact of rabies on wildlife

Wildlife are not only a vector of rabies (as witnessed by the role of the fox in sylvatic rabies in Western Europe), they can also be the victim of rabies. This is disastrous when the victim is an endangered species. Two striking examples come from Africa. The first concerns the Ethiopian wolf (*Canis simensis*) (26). Randall *et al*. describe a rabies outbreak in this endangered species, the world's rarest canid (27). The outbreak occurred in a sub-population of Ethiopian wolves in the Bale Mountains (Ethiopia) in 2003 and 2004. The Bale Mountains are home to around 300 of the global estimate of 500 Ethiopian wolves and they are closely monitored. Until August 2003, one area, the Web Valley, harboured an estimated 95 wolves. Over a six-month period, 74 individuals died or disappeared, instead of the expected 12. Thus, mortality clearly increased over this period. Over the same period, 32 cases of rabies were observed in domestic dogs and 20 cases in cattle. The rabies virus was diagnosed from 13 of 15 brain samples sent to the Centers for Disease Control and Prevention (CDC) in the United States. All available evidence suggested that domestic dogs were the reservoir for the virus; the genetic analysis identified the virus to be of canid type and no wildlife reservoir has ever been identified in Ethiopia. On the basis of several recommendations, the Ethiopian Wildlife Conservation Organization decided to intervene with a trial of parenteral vaccination. The results demonstrated the effectiveness of this type of intervention. However, with rabies-endemic dog populations around all Ethiopian wolf populations, further trials are required to ascertain the most reliable method of decreasing the rabies risk for each population of the species and to control any future outbreaks.

The second example is the African wild dog (*Lycaon pictus*) in Africa (28). The collapse and extinction of local populations of *Lycaon pictus* has been linked to pathogens of canine origin, such as the rabies virus (29, 30) and canine distemper virus (31, 32).

In addition, Blancou (33) reports the case in Namibia in 1977 of a cycle of non-bite-transmitted rabies that became established among the greater kudu antelope (*Tragelaphus strepsiceros*).

Other human interventions can have an indirect impact on rabies through wildlife. One such intervention is the use of diclofenac, a non-steroidal anti-inflammatory drug, to treat domestic livestock in Asia and Africa (34). For 15 years, diclofenac was available for veterinary use over the counter in pharmacies in Pakistan, India and Nepal. In these countries, it was widely used as a pain killer for the symptomatic treatment and management of inflammation, fever and painful conditions associated with disease or injury in domestic livestock. However, when it was applied empirically, diclofenac rarely resulted in a cure and many animals still died in spite of treatment. On the Indian sub-continent, it is customary to put out dead livestock for consumption by vultures and other scavengers. Vultures are exposed to diclofenac by consuming the carcasses of livestock that died within a few days of being treated with the drug. Vultures are extremely sensitive to diclofenac, which, even in very low concentrations, causes acute kidney failure and death. In South Asia, populations of the endemic Oriental white-backed vulture (*Gyps bengalensis*), slender-billed vulture (*Gyps tenuirostris*) and long-billed vulture (*Gyps indicus*) have declined dramatically by more than 95% since the early 1990s (35). These three species, which together used to number tens of millions, are now at risk of global extinction and are listed as 'critically endangered' by the International Union for Conservation of Nature. The disappearance of the scavenging vultures throughout the Indian sub-continent could lead to an increase in the number of feral domestic dogs, which are major vectors of rabies, a disease that kills up to 20,000 Indians (the majority of them children) each year (36). In the absence of vultures, the increased availability of carrion upon which feral dogs feed can be expected to boost their populations. It is reported that there has already been a 35% increase in the number of feral dogs in India.

Should the veterinary use of diclofenac in African countries result in a similar chain of exposure to vultures, it could quickly threaten the Cape vulture (*Gyps coprotheres*), which is already in grave danger of extinction, and would further threaten Rüppell's griffon vulture (*Gyps rueppellii*), the white-backed vulture (*Gyps africanus*) and the Eurasian griffon vulture (*Gyps fulvus*). In 2008, this threat led to the adoption of a resolution by the OIE Conference on Veterinary Medicinal Products in Africa ('Towards the harmonisation and improvement of registration and quality control'), which was held in Dakar (Senegal) in March of that year. The resolution, approved unanimously by the more than 160 Delegates present, called upon OIE Member Countries, taking into account their national situation, to seek measures to remedy the problem caused by the use of diclofenac in livestock.

Europe is suffering similar problems, albeit with less serious public health consequences. In July 2008, nine Eurasian griffon vultures were found dead in the French Pyrenees. They were lying close to the carcass of a cow that had been euthanised with a barbiturate containing the active principle pentobarbital. There had been other such incidents. The conservation of vultures in Europe remains fragile and incidents of this kind should be avoided at all costs. When carcasses of domestic animals are used to feed vultures (a measure that is conducive to their survival), they should be derived from animals killed in a way that will not be detrimental to the animals they are intended to protect. An article in the journal *Science* reports on a decline in the immune systems of vultures in Spain that had fed on the carcasses of antibiotic-treated livestock placed in *muladares* (special sites where the carcasses of domestic animals can be left for vultures to feed on). The authors of the study go so far as to advise against this practice which, up to now, has been seen as a conservation measure (37, 38).

Control of stray dog populations

As mentioned earlier, stray dogs are a health hazard in many countries (Fig. 1), not only to people (with dog bites responsible for a large proportion of human infections, especially in children) but also to domestic and wild animals. They pose an animal welfare problem too. With no owners, it is hard to gain access to stray dogs to conduct parenteral vaccination, for example. Immunisation using vaccines, as recommended in Chapter 2.1.13. of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*

Fig. 1
A stray dog close to a Masai village in Tanzania
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(*Terrestrial Manual*) is the preferred method for controlling rabies (39). However, it is vital for vaccination to be accompanied by effective stray dog control. Chapter 7.7. of the OIE *Terrestrial Animal Health Code* (*Terrestrial Code)* (40) states that a dog population control programme may have a variety of objectives; for example, it may aim to:

– improve the health and welfare of the owned and stray dog population

– reduce the number of stray dogs to an acceptable level

– promote responsible ownership

– assist in the creation and maintenance of a rabies-immune or rabies-free dog population

– reduce the risk of zoonotic diseases other than rabies

– manage other risks to human health (e.g. parasites)

– prevent harm to the environment and other animals

– prevent illegal trade and trafficking.

To achieve these objectives, stray dog population management measures for controlling (or eliminating) rabies should be accompanied by further control measures, including programmes to increase public awareness and education concerning dog ownership. A set of support measures is needed to ensure effective, long-term control of stray dog populations. Euthanasia of dogs, used alone, is not an effective control measure. Relevant control measures include the following:

– **Promoting responsible ownership.** Encouraging owners to adopt more responsible behaviour helps to reduce dog roaming and so limits risk to the community

– **Identifying and registering dogs.** Identifying and registering owned dogs, principally by establishing a centralised database, helps to improve law enforcement. Such measures also help to locate the owners of stray dogs

– **Controlling reproduction.** The reproductive control of dogs is essential to prevent the proliferation of stray dogs. Although this is essentially the responsibility of owners, public authorities should conduct awareness campaigns and, if possible, introduce incentives for owners to sterilise their companion animals

– **Regulating commercial dog dealers.** Dog breeders and dealers play a major role in promoting responsible ownership. Breeders' and dealers' associations should promote the objective of breeding and selling only dogs in good physical and mental health. The risk is that sick or aggressive animals may be abandoned by their buyers and join the stray dog population. Even if they are not abandoned, dogs with behavioural problems are more liable to wander and may attack people

– **Reducing dog bite incidence.** Awareness and education campaigns for the general public, dog owners and children can effectively limit the number of dog-related problems, including bites. Advice from dog behaviour experts is effective in reducing dog bite incidence

– **Euthanasia.** Euthanasia must be performed in accordance with the general principles in Chapter 7.7. of the OIE *Terrestrial Code* (40). The methods chosen must ensure operator and public safety. In addition, every effort must be made to prevent unnecessary pain and suffering for the animals being euthanised. To meet these requirements, operators must be properly trained and equipped and use the correct techniques. They must also ensure proper disposal of the carcasses of euthanised animals.

At the 77th OIE General Session in May 2009, the 174 OIE Member Countries unanimously adopted guidelines on stray dog population control, which are also in line with the recommendations for animal welfare in Chapter 7.1. of the OIE *Terrestrial Code* (41).

European regulation on international movements of companion animals

The fox rabies epizootic that swept through Europe in the 1960s prompted some European countries that had remained free of the disease, including the United Kingdom and Sweden, to introduce a six-month quarantine system to prevent the introduction of rabies. In the early 2000s, the improved epidemiological status of the entire European Union (EU) following a programme of oral vaccination of foxes led these countries to gradually abandon the quarantine system in favour of effective and less burdensome alternative animal health measures (Pet Travel Scheme). The improved situation also led the EU to regulate the non-commercial international movement of companion animals to prevent any risk of rabies being reintroduced into Member States that had become free of the disease (Regulation [EC]) No. 998/2003 of the European Parliament and of the Council of 26 May 2003). This EU regulation has been fully harmonised since 1 January 2012, when the United Kingdom, Ireland, Malta and Sweden aligned their rabies regulation with that applicable to the other Member States (Commission Implementing Decision of 15 December 2011 [notified under document C(2011) 9232]).

This regulation applies to international movements of dogs, cats and ferrets; the movements that are allowed vary, depending on the epidemiological status of the countries of origin and destination.

Commercial movements of companion animals (and non-commercial movements of more than five companion animals at a time) are subject to a separate regulation (Council Directive 92/65/EEC – Commission Regulation [EU] No. 388/2010).

Non-commercial movements between European Union Member States

Before dogs, cats and ferrets can be moved within the EU, they must have been vaccinated for rabies and have a microchip identification and a European model passport, as provided for in the annex to Commission Decision 2003/803/EC. Vaccination is valid 21 days after the first vaccine has been administered (in accordance with the primary vaccination protocol established by the manufacturer in the country where the vaccine is administered). A booster vaccination is valid immediately if the period of validity of the previous vaccination has not expired. The period of validity is that indicated in the manufacturer's instructions. Animals under the age of three months are generally not permitted to travel between EU Member States, but travel may be permitted under certain conditions defined by the national authorities.

Non-commercial movements from non-European Union countries

The regulation governing non-commercial movements between EU Member States also applies to certain non-EU countries with a favourable epidemiological status (countries listed in Annex II, parts B and C of Regulation [EC] No. 998/2003). Animals from these countries must be identified (e.g. with a microchip), vaccinated after the age of three months and hold an official health certificate in lieu of the EU passport.

For dogs, cats and ferrets entering the EU from a non-EU country with an unfavourable epidemiological status (including most African and Asian countries), the regulatory measures have been strengthened with a mandatory pre-entry check on the efficacy of the rabies vaccination. A blood test for rabies antibody titration must be performed by an authorised veterinarian at least 30 days following the animal's vaccination and three months before it is moved to the EU Member State. This three-month waiting period following the blood test reduces the risk of importing an animal that is incubating the disease, as vaccination during the incubation period does not prevent the disease.

Rabies antibody titration is one of the two variants of a serum neutralisation test prescribed by the OIE *Terrestrial Manual* (fluorescent antibody virus neutralisation and rapid fluorescent focus inhibition test) and must be performed by an EU-accredited laboratory (39). Neutralising antibody levels at or above 0.5 International Units per millilitre of serum are indicative of post-inoculation immunity.

This serological test does not need to be repeated for subsequent journeys if the animal has received booster vaccinations within the time limit prescribed by the vaccine manufacturer.

Before a companion animal living in the EU may be moved to a non-EU country with an unfavourable epidemiological status, vaccination followed by a serological test after 30 days must be performed prior to departure. However, for the return journey to the EU, the three-month waiting period following the blood test is not required.

The costs and benefits of rabies control measures

Rabies – and the control and prevention measures introduced to combat it – have a significant impact on infected countries. An estimate was made of the cost of rabies to Belgium of a fox rabies epizootic in the 1980s. The combined cost of post-exposure vaccinations of people, surveillance, laboratory diagnosis, preventive vaccination of people at risk, farmer compensation for the slaughter of infected livestock and fox culls (gassing burrows and cash payments for the tail of each fox killed) was estimated at 40,000 old European Currency Units (ECUs) per year per thousand square kilometres (42). This estimate of costs to the State did not include the labour costs of officials involved in the control and prevention operations. Neither did they include preventive rabies vaccination of dogs, which was made mandatory throughout the infected area. Dog owners were responsible for paying the costs of the latter animal health measure (vaccines and consultation with a veterinarian).

The objective of a programme of oral vaccination of foxes is not to control rabies but to eradicate it. It has been shown that this objective can be achieved by implementing three successive fox vaccination campaigns, conducted at approximately six-month intervals and by adopting an appropriate strategy for the distribution of vaccine baits (42, 43). In Belgium, the estimated cost of three vaccination campaigns was 60,000 old ECUs per thousand square kilometres in the late 1980s (42). Compared with the annual cost of the prevention and control measures described above, this vaccination strategy proved to be beneficial in the short term and constitutes an investment. A cost/benefit study conducted in France also showed that the cumulative annual costs of the two strategies (oral vaccination and culling) were comparable until the fourth year, after which the oral vaccination strategy became more cost-effective (44).

Vaccines and rabies vaccination

Chapter 2.1.13. (Rabies) of the OIE *Terrestrial Manual* (39) describes the characteristics of vaccines for immunising domestic animals. Rabies vaccines prepared from Pasteur's original 1885 strain and its derivative strains, and strains isolated more recently (Flury, Street-Alabama-Dufferin [SAD], Vnukovo and Kelev) protect against all genotype 1 strains isolated to date. Conventional rabies vaccines do not confer adequate cross-protection against other lyssaviruses, especially those in phylogroup 2. They provide no protection against Mokola virus (45) or West Caucasian bat virus (46). Cross-neutralisation and cross-protection have been demonstrated using conventional rabies vaccines against two viruses belonging to phylogroup I, one of Eurasian origin and the other of Australian origin (47). The principles for the preparation of inactivated rabies vaccines are the same, whether the vaccines are for use in humans or animals. Recombinant vaccines such as recombinant vaccinia-rabies vaccine have also proved to be effective. As these vaccines contain no attenuated rabies virus, animals immunised with recombinant vaccine should be exempt from any import ban by countries restricting imports of animals immunised with attenuated vaccine. As recombinant and attenuated vaccines are effective for oral use, they can be distributed in bait to immunise wildlife. Standards for vaccines containing attenuated rabies virus strains differ from those for vaccines prepared using inactivated virus. While each type of vaccine has its advantages and drawbacks (47), both can be used to immunise animals for a period of one to three years. In veterinary medicine, they cannot be used curatively (48).

However, preventive vaccination of dogs is recommended in countries where canine rabies is widespread (49), especially developing countries and emerging economies (50, 51). Most vaccination campaigns manage to achieve the recommended WHO target of at least 70% coverage of the population, with an observed coverage of 76.5% in urban areas and 73.7% in rural areas. However, at present, vaccination campaigns do not appear to be organised in the countries most affected. What is more, the majority of dogs in developing countries are very young and have a short lifespan, reducing the effectiveness of vaccination campaigns. Nevertheless, such vaccination campaigns have shown that, to protect public health, it is always best to tackle rabies at source. To this end, rabies vaccine banks are being set up under OIE supervision, particularly in Asia. In countries currently free from urban and sylvatic rabies, the main goal is still to prevent reintroduction, especially as a result of smuggling (52). According to Chapter 8.11. of the OIE *Terrestrial Code* (53), a country may be considered free from rabies when:

– the disease is notifiable and any change in the epidemiological situation or relevant events are reported to the OIE

– an ongoing system of disease surveillance has been in operation for the past two years, with a minimum requirement being an ongoing early detection programme to ensure investigation and reporting of rabies-suspect animals

– regulatory measures for the prevention of rabies, including measures covering the importation of animals, are implemented in line with the recommendations in the OIE *Terrestrial Code* (53)

– no case of indigenously acquired rabies virus infection has been confirmed during the past two years

– no imported case in the orders Carnivora or Chiroptera has been confirmed outside a quarantine station for the past six months

– imported human cases of rabies do not affect rabies-free status.

Development and use of a recombinant vaccinia-rabies virus for the oral vaccination of wildlife

The term 'rabies vector' refers to the animal species most susceptible to the rabies virus in a given area at a given time: the species solely responsible for maintaining the infection. All other species (including humans) are considered to be rabies victims, even if they are capable of transmitting infection; consequently, destroying or immunising them has no effect on the epidemiological cycle of the disease. While rabies can be effectively controlled in domestic animals by taking appropriate control measures, this is not the case when it comes to controlling the infection in wildlife. Until the early 1980s, the sole method considered was to reduce the vector population (54). However, the limitations of this method soon became clear and the oral immunisation of wildlife began to be considered as an alternative (55). The vaccination of wildlife against rabies was a method developed first in the United States (56) and later in Europe (57). It was used for the first time in the field in Switzerland in October 1978 (58). The earliest vaccine strains were attenuated strains of rabies virus, but subsequent developments focused on recombinant strains. They included a recombinant vaccinia virus (Copenhagen strain) expressing the rabies virus glycoprotein (59). A recombinant vaccinia-rabies virus provides a real link between Edward Jenner and Louis Pasteur (60). This recombinant vaccine was first tested in foxes in an experimental station, where it proved to be totally effective (61, 62), as well as in the raccoon dog, another vector of rabies in Europe. Its efficacy and safety were also tested by administering it orally to dogs and cats (63). As this vaccine was intended for field use, its safety was confirmed in many non-target species sharing the same ecosystem with the fox and raccoon dog in Europe, including the badger (*Meles meles*) and wild boar (*Sus scrofa*) (64). A system for administering the recombinant virus in bait was then developed (65). The same trials were performed in the United States, in particular on the raccoon and skunk (66, 67). The first field trials in administering the recombinant vaccinia-rabies vaccine were held in Belgium (68), first on a small scale and later on a larger scale (69). Later, the full-scale use of this oral vaccine led to the eradication of fox rabies from Belgium (70) and other European countries. Similarly, in North America the use of this vaccine brought rabies under control in such vectors as the fox, raccoon and coyote, but not the skunk.

In conclusion, several vaccination campaigns are enough to eradicate sylvatic rabies locally, provided that they involve the use of: an effective, safe and stable vaccine; a system of effective and resistant baits; a safe and convenient method of delivering baits; and an effective scheme for distributing baits in time and space (43).

The role of international institutions and conclusions

The main international and national organisations involved in rabies control are also those behind the One Health concept: OIE, WHO and FAO, assisted by the European Centre for Disease Prevention and Control, CDC in the United States, and the reference laboratories of various organisations, and supported by donors such as the European Commission and the World Bank.

With the support of these organisations, there is every hope of one day eradicating terrestrial rabies at its source in animals, which will bring enormous public, animal and environmental health benefits.

■

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