Rabies elimination in Europe – A success story

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Summary

The current rabies situation in Europe is probably unprecedented in history. Large parts of Western, Northern and Central Europe are officially recognised as free from terrestrial rabies. This achievement is the result of step-by-step intensive efforts to control and eliminate both urban (canine) and sylvatic (wildlife-mediated) rabies. Although canine rabies was already successfully controlled through the strict implementation of hygiene measures in several European countries at the beginning of the 20th Century, Europe-wide elimination was accomplished by registration and mass vaccination of dogs in the 1970s. In contrast, the emergence of fox rabies in the 1940s as the result of a transition from urban to sylvatic rabies posed a new challenge and required fundamental changes in rabies control policies. Early attempts to control fox rabies, aiming at a drastic reduction of the fox population to interrupt the infectious cycle, failed and were suggested as being counter-productive. An increasing rabies incidence required alternative rabies control methods. In the 1970s, the concept of oral rabies vaccination (ORV) offered a new perspective for rabies control in wildlife. However, appropriate tools had still to be developed from scratch. Pioneering developments, including efficacious and safe oral rabies virus vaccines, adequate vaccination strategies, machine-made baits and automated aerial bait distribution, were technical milestones on the road to success. Since 1989, the European Union (EU) has become the driving force for fox rabies control in Europe via its policy of co-financing the costs of disease eradication. Despite the tremendous success achieved, European countries have had to face several setbacks, resulting in a delay in rabies elimination at the regional level. The reasons for these setbacks were multifaceted and lessons had repeatedly to be learned. In Western Europe, all measures are directed towards the maintenance of a rabies-free status by avoiding the reintroduction of the disease through measures including the implementation of the companion animal travel scheme, risk-based surveillance and the establishment of cordon sanitaires *along the borders of*

rabies-endemic regions. Since the complete elimination of rabies from Europe has not yet been achieved, the EU has spent more than 75 million Euros (€) to support rabies elimination in Turkey, the Western Balkan region, Kaliningrad and neighbouring third countries to the north east.

Keywords

Case study – Europe – Dogs – Foxes – Oral vaccination – Parenteral vaccination – Rabies.

Introduction

Zoonotic RNA viruses play an increasing role in emerging human diseases on a global scale (6, 10, 26, 40, 55). Social and environmental changes open ecological niches that promote rapid selection of novel virus variants (26, 27, 31). Furthermore, some RNA viruses have the ability to alter their animal host range, which may also include humans. Among these pathogens, the causative agents of rabies are prime examples (10). Rabies is one of the oldest recognised zoonoses, defined as acute, progressive incurable viral encephalitis (28). Disease distribution encompasses all continents, with the exception of Antarctica. Recognised aetiological agents are negative-strand RNA virus species (previously genotypes) of the *Lyssavirus* genus, family *Rhabdoviridae,* of the *Mononegavirales* order (www.ictvdb.org/Ictv/index.htm) (24, 33, 37). Although susceptible natural hosts include all mammals, primary reservoirs reside in the orders *Carnivora* and *Chiroptera*. This plethora of viral variants presents a formidable challenge to a strict basic concept of true disease eradication (50). Of the 14 lyssavirus species known, the rabies virus (RABV) is the most important one, maintained by a diversity of abundant carnivorous and viverid hosts across the world and *Chiroptera* in the Americas (61).

While fox- and dog-mediated rabies is diminishing in Europe and Latin America, the disease remains a major threat to more than two-thirds of the world's population living in rabies-endemic areas in Africa and Asia. Here, more than 90% of the estimated tens of thousands of annual human rabies deaths occur (61). Canine rabies poses the biggest public health problem and 99.9% of rabies deaths are the result of transmission caused by dog bites. Furthermore, dog bites are responsible for millions of suspect exposures, causing fear and tremendous costs from post-exposure prophylaxis (PEP), if available. Reducing the cost of PEP and preventing administration delays is important, particularly in resource-limited settings (25).

All figures are likely to be underestimates, due to the widely recognised under-reporting and misdiagnosis of the disease in humans in developing countries, and the true burden of human rabies is estimated to be much higher. This is supported by a detailed hospital-based study in Malawi, where 11% of all childhood encephalitis cases were caused by rabies, and childhood rabies was commonly misdiagnosed as cerebral malaria (36). Without the use of preventive intervention, i.e. PEP, the total number of predicted human rabies deaths in Asia and Africa would even be in the hundreds of thousands (30).

Although it is deemed essential that any rabies control strategy should be considered in both its veterinary and medical context (22), improving PEP delivery alone does not offer a long-term solution to control the disease. Without controlling rabies at the animal source, the incidence of human exposures will continue to rise and the high costs of PEP needed to prevent human deaths in bite victims will rapidly become unsustainable (34). Technically and logistically, the elimination of human rabies is a realistic goal for developed and underdeveloped countries alike, through control of terrestrial rabies and adequate administration of PEP. Where vaccination coverage has been sufficient to control rabies in carnivorous reservoir species, a well-designed rabies eradication programme leads to reduced virus transmission and immediate public health and economic benefits. Therefore, a radical

'paradigm shift' in strategic planning and implementation of measures is required in the many countries still focusing on PEP as the only means to prevent human deaths. Rabies could serve as a practical approach and 'hands-on' example to facilitate the application and accelerate the necessary leverage of 'One Health' (63).

As distinct terrestrial RABV variants are known to be maintained within single animal reservoirs in a geographic area, e.g. dog-, fox-, raccoon-, skunk-mediated rabies, etc., elimination is possible by targeting control strategies to the specific reservoir host (61). A prime example for successful rabies control at the animal source is Europe (58). Therefore, this report aims at describing Europe's efforts, milestones, achievements and setbacks in controlling animal rabies, as well as future plans and roadmaps to eradicate fox rabies.

Elimination of canine rabies

The history of rabies in Europe includes both canine and wildlife rabies. Although no figures exist for the true incidence of rabies in past centuries, historical reports available from various parts of the continent give at least a rough idea of the extent to which this disease posed a threat in ancient times. Whilst dogs and wolves were initially the greatest rabies threats in continental Europe, in the 20th Century fox rabies became the most important challenge (8).

Canine rabies (also referred to as urban rabies) had been present for centuries. Historically, dogs had been recognised as the source of infection and control efforts had been in place for hundreds of years (46). Specific dog movement restrictions and muzzling were the only measures applied on a large scale in European countries at the beginning of the 18th and during the 19th Century. Early legislation to control rabies in dogs and cats is known to date back to 1875 and 1880, in the Netherlands and Germany, respectively (4, 44). From 1875 until the 1950s, additional rabies control measures, such as stray dog elimination, enforcement of sanitary policy, quarantine, notification of rabies, tracing movements of rabid dogs and their contacts, as well as strict import regulations, were implemented in many European countries. These simple but strict sanitary measures were able to substantially control urban rabies and, as a result, freedom from dog-mediated rabies was achieved in some areas in Europe, including Scandinavia (pre-1900), Denmark (1889), Austria (1914), Germany (1914, 1939), the United Kingdom (1922) and the Netherlands (1923), at the beginning of the 20th Century (4, 23, 41, 43, 44, 56).

Substantial technical progress achieved in the first half of the 20th Century led to the development of safe, affordable and efficacious inactivated animal rabies vaccines. Hence, during the 1930s to the 1980s, the application of mass (sometimes compulsory) vaccination of dogs, together with dog registration, collection of ownership tax and movement restrictions, became a cornerstone in dog rabies control at the European level, resulting in a declining disease burden in further European countries within a few decades. The former Czechoslovakia and Hungary were the first countries to eliminate urban rabies using this new concept in the 1930s and 1940s, respectively (35, 38). In the subsequent two decades, France (1960), Italy (1973), and Spain and Portugal (1975–1978) achieved freedom from dog-mediated rabies on their territories, whilst Greece and the former Yugoslavia only followed in 1987 and 1991 (1, 4, 45). So, from a veterinary and medical standpoint, the successful elimination of canine rabies in many European countries has been witnessed in the last century, along with growing confidence that it will no longer present a major threat to public health in these countries. In Europe, dog-mediated rabies persists only in Turkey (29). However, in the past, despite the implementation of strict measures on the non-commercial movement of companion animals within and into the European Union (EU), sporadic cases of dog rabies have been reported in rabies-free regions, as a result of illegal dog importations from rabies-endemic countries (29).

Re-emergence of rabies in wildlife

Whilst strict implementation of mass vaccination and hygienic measures resulted in a virtual disappearance of dog-mediated rabies in Europe, the disease unexpectedly re-emerged in wildlife in the 1940s, i.e. in red foxes (*Vulpes vulpes*), for reasons that are not fully understood. The epidemic of fox rabies that followed, also referred to as sylvatic rabies, is believed to have started in a focus south of Kaliningrad during World War II, probably as the result of a sustained spillover from domestic animals (54). Recent molecular characterisation of RABV isolates from the former Soviet Union, however, revealed the existence of RABV lineages in the Asian part of Russia that may question this hypothesis for the origin of the epidemic (32). In any case, historical evidence suggests that the prevailing conditions must have favoured virus perpetuation and maintenance in red foxes, as RABV strains adapted to the physiological traits and population biology of their new host and developed a host-specific pathogenesis and pathogenicity (58). As a result, the disease quickly became established and the red fox became the new main reservoir for rabies in Europe, inexorably spreading the disease across the continent within a few decades (54). By the mid-1970s, large parts of Central and Western Europe were affected (Fig. 1) (58). Measures successfully implemented in the past to control urban rabies failed to stop the spread of fox rabies, and thus the change from urban to sylvatic rabies posed a new challenge for wildlife rabies control and required substantial changes in control policies (59). Early conventional control measures were aimed exclusively at decimating the fox population by intensive culling, destruction of fox cubs at dens, poisoning, gassing and hormonal sterilisation. These attempts to interrupt the disease transmission within fox populations had variable success on the local level. In fact, it became exceedingly difficult to reduce fox population densities to levels (R_0) at which the social networks of the animals ceased to operate and transmission was interrupted ($R_0 < 1$) (3, 58). Moreover, these measures were regarded as counter-productive since they disrupted the social system, thereby increasing contacts between foxes and, hence, the rabies incidence. As a result, the number of reported rabies cases steadily increased across Europe until the 1980s, when fox rabies reached its western- and south-eastern expansion in Europe. With 24,390 and 22,588 reported rabies cases in wildlife and domestic animals, the rabies incidence in Europe reached peaks in 1984 and 1989, respectively (Fig. 2). Between 1977 and 2010, a total of 217 human rabies cases were reported in Europe. The great majority of these could be attributed to fox-mediated rabies acquired in affected European countries (Rabies Bulletin Europe [WHO]).

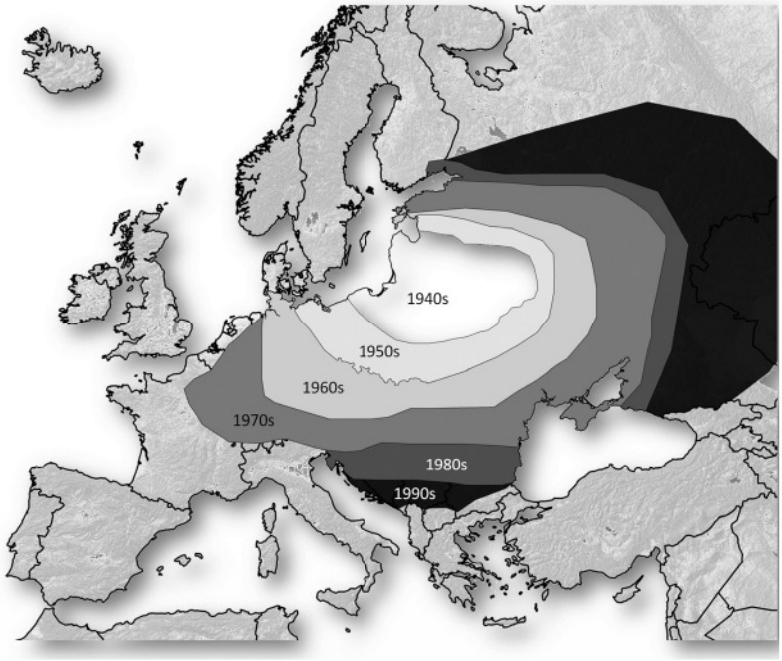

Fig. 1
Assumed spread of the fox rabies epidemic in Europe during the 20th Century

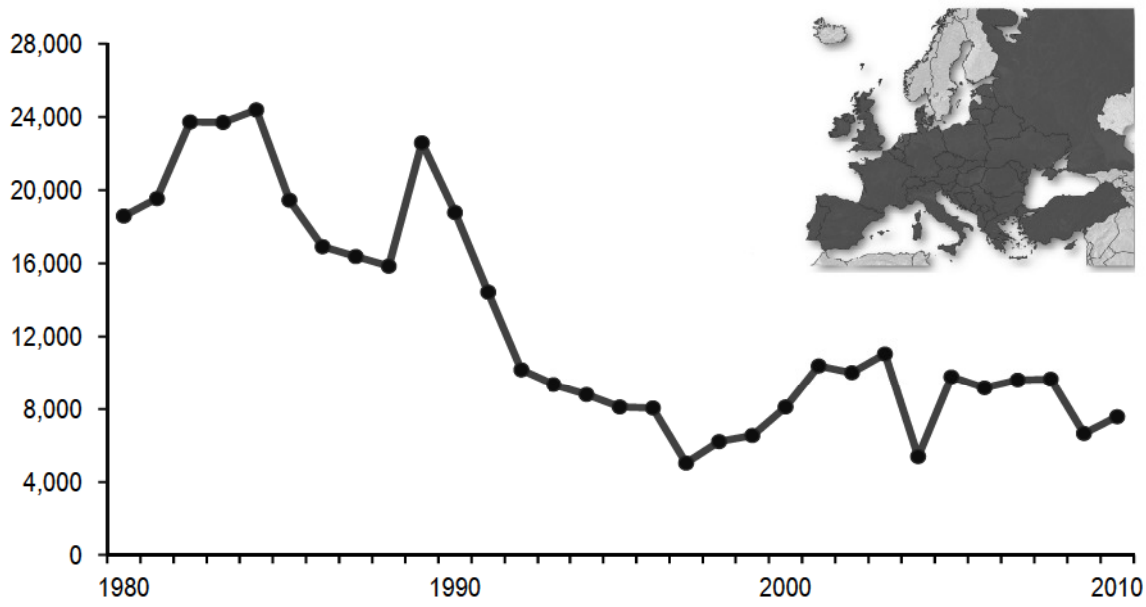

Fig. 2
Development of the total number of rabies cases in animals in Europe from 1977 to 2010, as officially reported to the database of the Rabies Bulletin Europe
The map in the upper right corner indicates countries that reported rabies cases during this period

Technical and political milestones in the implementation of oral rabies vaccination of foxes

The steadily increasing rabies incidence in the 1970s and 1980s demanded the rapid implementation of alternative wildlife rabies control strategies in Europe. Early innovative research had already shown in the 1970s that red foxes could be immunised by the oral route against rabies, using attenuated rabies viruses (5, 7). These promising experimental results led to the concept of oral vaccination of wildlife (ORV) against rabies using modified live virus vaccines, and suddenly offered the solution for control strategies for sylvatic rabies (57). So, it appeared feasible to create an immune barrier in the wildlife reservoir species and vaccinate a sufficiently large proportion of foxes to interrupt the spread of the disease, a finding that was predicted intuitively (58). Before the theory could be turned into practice, however, many other problems needed to be solved for the successful implementation of ORV under field conditions. As well as a bright idea and an experimental approach, a potent and safe oral rabies virus vaccine (either attenuated or recombinant) and basic principles for a vaccination strategy, including timing, bait density, duration, surveillance and monitoring, also had to be developed. The first ORV field trial, conducted in Switzerland in 1978, proved the concept under field conditions and triggered further field trials in other European countries in subsequent years (52). The development of machine-made baits, the implementation of aerial distribution of baits and of computer-supported, automatic dropping devices were further technical milestones that allowed the implementation of large-scale vaccination campaigns (48). However, it was not only these technical advances but also political milestones that were a prerequisite for turning field trials into real ORV programmes.

First of all, the pioneering spirit and commitment of researchers and workers in a few countries, e.g. Switzerland, Germany, France and Belgium, must be mentioned. It took leadership in research on attenuated rabies virus vaccines, ORV strategies and related issues at the time, something that is unfortunately often missing when ORV programmes are implemented nowadays or technology

transfer is conducted. The World Health Organization (WHO) and the World Organisation for Animal Health (OIE) committed themselves to and strongly supported this work by appointing expert committees and sponsoring informal meetings and scientific conferences where information could be exchanged, guidelines for future research discussed and recommendations for ORV programmes given. Since the end of the 1980s, the European Community (EC), later succeeded by the EU, has become the driving force in fox rabies control in Europe via its veterinary fund, which co-finances the costs of Member States of the EU for disease eradication. First support from the EC to ORV was granted in 1989, with funding of up to € 10,000 for small-scale pilot projects in regions where non-governmental organisations distributed baits free of charge (18). Soon after that, Council Decision 90/424/EEC of 26 June 1990 on expenditure in the veterinary field (recently replaced by Council Decision 2009/470/EC) was a milestone and breakthrough for fox rabies control in Europe, as it included rabies in the list of animal diseases for which Member States could receive Community financial support for their national programmes (16, 19).

This offered a financial incentive for the implementation of large-scale ORV pilot programmes in Member States. For approved programmes, 50% of the costs for purchasing vaccine baits and bait distribution were subject to reimbursement. Strong back-up from international public and animal health organisations, as well as the financial incentive from the EU, resulted in strong and long-term commitment from many West European governments, which provided a basis for the successful implementation and long-term funding of national rabies eradication programmes. The EU even stimulated the implementation of ORV programmes in neighbouring non-EU countries by co-financing a 100-km-wide vaccination belt along common borders, if a comparable ORV programme was in place and the adjacent Member State was able to make an interim payment of 50% of the costs to the neighbouring country. In 2002, the EC published a set of recommendations for oral vaccination implementation in Europe, passive surveillance and monitoring of oral vaccination campaigns (14). To avoid the reintroduction of rabies from endemic countries, and to help make rabies elimination efforts in wildlife in EU Member States sustainable, the EU harmonised the non-commercial movement of companion animals within and into the EU in 2004. Regulation 998/2003 lays down risk- and science-based requirements for the movements of pet dogs, cats and ferrets, which include microchipping, documentation, vaccination and, depending on the origin of the animal, an antibody titration test (20). In 2003, the EU also established a rabies subgroup under the Task Force for Monitoring Animal Disease Eradication, dedicated to assessing co-financed ORV campaigns in Member States and regions of neighbouring non-EU countries. The recommendations of the subgroup to improve implemented ORV programmes in Member States are publicly available. In 2008, an EU Reference Laboratory for Rabies was designated, which particularly aims at harmonising and standardising diagnostic techniques throughout the EU (15).

Impact of oral rabies vaccination of foxes in Europe and lessons learned

Since the first fox ORV field trials conducted in Switzerland in 1978, ORV has become the method of choice for fox rabies control in Europe. During the past 33 years, 24 European countries implemented ORV programmes on their territories. The maximum total area ever covered, at least once, with vaccine baits in Europe between 1978 and 2010, encompassed almost 1,911,900 km² (Fig. 3). By the time of the 2004 enlargement of the EU, almost all the 'old' EU Member States (the EU-15) were free from rabies in terrestrial animals. Following the enlargements of 2004 and 2007, a number of eastern European 'new' EU Member States gained access to EU veterinary funding and were able to initiate ORV programmes or intensify and expand their ORV programmes which were already in place (13). The implementation of ORV programmes in European countries also benefited from the experience gained in the past. In most cases, it resulted in a spectacular improvement of the rabies situation, with a sharp decrease in reported rabies cases and the virtual disappearance of the disease

in large, previously infected areas, sometimes within a relatively short period of time, especially in sparsely populated areas, e.g. in Estonia (47).

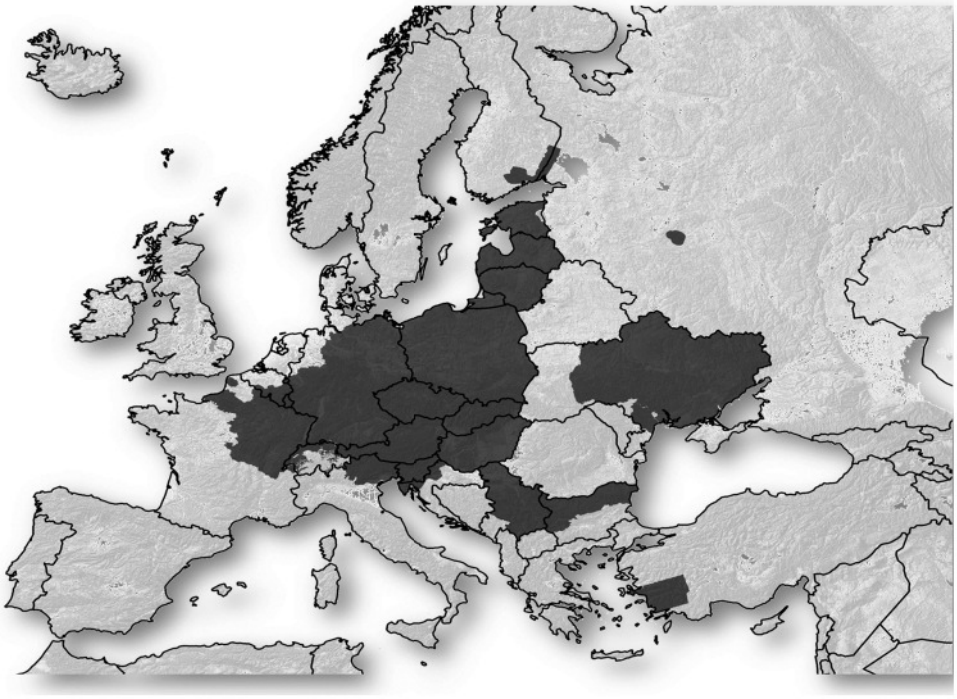

Fig. 3
Area covered with oral rabies vaccine baits in Europe between 1978 and 2010

The number of animal rabies cases in Europe decreased from 22,588 in the year with the highest peak (1989) to 7,589 cases in 2010, a decrease of 66% (Fig. 2). To date, ten European countries have been officially recognised as being free from rabies in terrestrial animals due to ORV, i.e.: Finland (achieved rabies-free status in 1991), the Netherlands (1991), Italy (1997, but lost status in 2008), Switzerland (1998) (62), France (2000, regained status again in 2010 after having lost it in 2008), Belgium and Luxembourg (2001), the Czech Republic (2004) (11, 39) and Germany and Austria (2008) (2). However, the disease remains a threat in Eastern Europe and in the Balkans. The latter was the source of a recent emergence of fox rabies in Italy in 2007, after it had been free from sylvatic rabies for more than a decade (12). Only emergency vaccination measures, including vaccinating areas at higher altitudes, eventually brought this epidemic under control (9, 42).

Despite the tremendous success achieved, European countries have had to face several setbacks that resulted in a greater or lesser delay in rabies elimination at the regional level (53). During the 1980s and 1990s appropriate tools had to be developed 'from scratch' to respond adequately to the changing rabies situation. However, the vaccine baits or the vaccination strategy were often questioned. In fact, it turned out that human error was very often one of the critical points because, after their initial success, setbacks in rabies control in many European countries were often the result of a self-acting process. With regard to ORV, human error is mainly due to a wrong situation assessment and inadequate response (49). The reasons for such setbacks were mostly multifaceted management problems, involving:

i) planning (a special rabies situation, adequate long-term funding)

ii) communication (awareness, chain of command, information exchange)

iii) quality control (vaccine production/titres, vaccine thermostability, aerial distribution, cold chain of vaccines)

iv) sub-optimal ORV strategies (common national strategy approach, complementary measures, cross-border activities)

v) epidemiological supervision (over-optimistic appraisal of initial success, adequate rabies surveillance, monitoring of ORV, data management) (50).

Other factors that could have had a negative effect on the success of ORV campaigns were increasing fox densities and, often, other disease priorities. Countries that disregarded experience and scientifically validated recommendations unfortunately often made the same mistakes that had been made in the past, and lessons had to be learned repeatedly (50).

The European way forward

Although WHO believed in 1990 that rabies in foxes could be eliminated throughout Europe by the end of the 1990s using ORV (60), at the beginning of the 21st Century, complete elimination of the disease has still not been achieved. In Western Europe, all measures are directed towards the maintenance of a rabies-free status by avoiding the reintroduction of the disease. This approach includes implementing rules for the movement of companion animals, risk-based surveillance and the establishment of *cordon sanitaires* along the borders of rabies-endemic regions. However, the disease continues to be a threat in the Balkans and Eastern Europe. Yet again, it is the EU that has taken the initiative and become the driving force behind the scene. Since the gradual but complete eradication of terrestrial rabies from the EU appears to be feasible in the short or medium term, the EU is giving top priority to rabies control. To encourage Member States to eliminate rabies from their remaining infected territories, by implementing non-interrupted ORV campaigns despite a difficult budgetary situation, the European Commission has increased its support in co-financing ORV programmes from 50% to 75% since 2010 (17, 21).

However, in most Member States that share land borders with non-EU countries where rabies is still present in wildlife, elimination of the disease would be impossible to achieve or maintain, as the reintroduction of rabies from adjacent regions is inevitable. The European Commission, together with the affected Member States, identified the need for action very early on and began entering into negotiations with neighbouring non-EU countries at the end of the first decade of the 2000s (13). Since 2007, the EU has financially supported ORV campaigns in various neighbouring non-EU countries. Between 2007 and 2010, the EU has, for example, spent more than € 13 million on developing a sustained EU-compliant rabies control system in Turkey, with the main focus on eliminating dog rabies, and to ensure a human and animal health status similar to that in the EU. After a recent sustained spill-over event from dogs to foxes and the subsequent rapid spread of fox rabies, the EU has, since 2008, covered the costs for the purchase of vaccine baits to vaccinate an area comprising 36,847 km² in the Aegean region of the country. Next to Turkey, the EU has also emphasised its commitment to supporting rabies control in the Russian region of Kaliningrad, the Western Balkans and in north-eastern neighbouring countries. Since 2008, the financial support given by the EU to ORV campaigns in Kaliningrad has already resulted in a significant improvement in the disease situation in neighbouring Member States. The sum allocated to the Kaliningrad ORV programme for the period between 2008 and 2011 was € 1.8 million and the same amount of money has already been approved for a further three-year period. As endemic terrestrial rabies in the Western Balkans would pose a permanent threat to ORV programmes in Slovenia, Hungary, Romania and Bulgaria, then, from a public health and economic point of view, supporting efforts to eliminate rabies in this region would be a far better solution in the long term.

In the framework of the Instrument for Pre-accession Assistance (IPA), destined for candidate or potential candidate countries for accession to the EU, it is possible to support eradication activities for certain animal diseases in this region, including rabies. These activities consist of two components:

a national one, comprising seven separate national projects that include ORV, technical assistance and public awareness activities, and a regional one, aimed at reinforcing cross-border cooperation and contributing to the harmonisation and coordination of ORV campaigns at a super-regional level. By the end of 2011, most Western Balkan countries are expected to have commenced the implementation of ORV in their territories. From 2008 to 2013, an IPA budget of about € 55 million is expected to be needed for rabies eradication in the Western Balkans. To address the rabies threat from north-eastern neighbouring countries, e.g. the Russian Federation, Ukraine and Belarus, the Commission has encouraged interested Member States to develop agreements with their neighbours to include ORV activities in the territories of the latter, along common borders, within their own EU co-financed ORV programmes. For 2011, ORV in those areas of the Russian Federation that border Finland and the areas of Belarus that border Lithuania has been approved for 100% EU funding. Depending on the conclusion of bilateral agreements, further non-EU areas that border EU Member States are envisaged to start ORV under this scheme by the year 2012 or later. When fully implemented, the expenditure for these activities in those countries is estimated at € 5 million in total per year (13).

Conclusions

Oral rabies vaccination of foxes is the first example of a modern and innovative method of disease control in wildlife. The tremendous success achieved in Western and Central European countries during the past 30 years raises reasonable hope for the elimination of fox-mediated rabies at the European level. Thanks to the strong financial and political commitment of the EU, further European countries are expected to eliminate rabies from their territories in the near future. However, considering the huge areas that would have to be vaccinated, in particular in Eastern Europe, rabies elimination will be a true challenge in these countries, not only from a logistic but also from an economic point of view (50). Since rabies is a transboundary zoonosis, we cannot just leave it to these countries to solve the problem. As access to sufficient long-term funding is of the utmost importance in achieving the long-range goal of eliminating terrestrial rabies (51), the coordination of ongoing ORV programmes should be strengthened, on the one hand, and joint international efforts should be undertaken to develop new approaches for cost-effective vaccination strategies, on the other.

Recommendations

As rabies in wildlife reservoirs still remains important in many parts of Europe, all European governments should continue to classify rabies as a high-priority disease. Since rabies is a transboundary disease, combined efforts are needed to eliminate it in Eastern and south-eastern Europe.

A large-scale and long-term ORV approach has been shown to be highly efficient and cost-effective in the long run. Therefore, sufficient long-term funding is of the utmost importance in achieving long-term programmatic goals in eliminating rabies.

Countries which have implemented or which are going to implement ORV programmes on their territories should carefully consider the 'lessons learned' from other European countries to avoid unnecessary setbacks and additional costs in rabies elimination.

Considering the huge rabies-affected areas of Eastern Europe, rabies elimination using ORV in these countries would require new scientific solutions as well as fresh logistical and strategic approaches.

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