Rabies Control –
Towards Sustainable Prevention
at the Source

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# Contents

### Acknowledgements

3

### Foreword

7

## The reality of rabies: setting the scene

Global perspective of rabies

A.I. Wandeler

9

Towards sustainable prevention of rabies at the source: a case report from India

S. Abdul Rahman

17

Rabies in China

C. Tu

25

Rabies elimination in Europe – A success story


31

Epidemiological factors and control of rabies in North Africa

M. El Harrak

45

Rabies and rabies control in African regions

L.H. Nel, T.P. Scott, N. Wright, N. Mollentze, W. Markotter, C.T. Sabela & K. le Roux

51

Epidemiology of rabies in Korea


59

Epidemiology of rabies in Bhutan: geographical information system-based analysis

T. Tenzin, M.P. Ward & N.K. Dhand

67

### Scientific advances: current and future tools available for rabies control

Molecular tools for rabies diagnosis in animals


75

Criteria for parenteral and oral immunisation of dogs against rabies

C.L. Schumacher

87

Immunoncontraception as a tool for rabies and canine population management

C.E. Rupprecht, X. Wu, R. Franka, T. Smith & D. Slate

95

Canine adenovirus antibodies in meso-carnivores in the United States of America: implications for oral rabies vaccination using recombinant adenovirus vaccines?


109

### Economic dimensions of rabies control

Impact of animal rabies on local economy

K. de Balogh, M. Dominguez, S. Zombou, J. Siembieda, N. de Haan & J. Zingeser

117

Cost of national wildlife rabies elimination programmes

H.-J. Bätza

123
International standards and regulatory framework

World Organisation for Animal Health standards and scientific activities for rabies control ............. 127  
L. Knopf, Y.J. Kim & E. Erlacher-Vindel

Rabies control: other relevant international standards and policies ........................................................ 135  
C. Machalaba & W.B. Karesh

Role of various stakeholders in rabies control in the animal reservoir

Local governments, municipalities and dog rabies control ................................................................. 145  
K. Le Roux & L.H. Nel

Rabies control and animal welfare ........................................................................................................ 151  
H. Eckman, S. Vallentine & E. Hiby

Awareness and communication programmes for eliminating rabies at the animal source ............... 157  
P. Costa, L. Taylor & D.J. Briggs

New approaches in dog rabies control programmes

The economics of dog rabies control and the potential for combining it with other interventions ...... 163  
J. Zinsstag, M. Lechenne, R. Mindekem, S. Naissengar & E. Schelling

Assuring the quality and sustainability of a rabies dog vaccination programme:  
vaccination, rabies surveillance and post-vaccination monitoring ..................................................... 169  
F. Cliquet & J. Barrat

Public and private funding sources for sustainable rabies control programmes ................................ 177  
M.E. Miranda, N.L.J. Miranda & D.J. Briggs

Catch, inject and release: immunocontraception as an alternative to culling  
and surgical sterilisation to control rabies in free-roaming dogs ...................................................... 181  
G. Massei

Strategies today and tomorrow at the animal source

Mainstreaming rabies prevention and control at the national level:  
a focus on the role of national Veterinary Services ............................................................................ 189  
G. Brückner

OIE activities to support sustainable rabies control:  
vaccine banks, OIE twinning, and evaluation of the performance of Veterinary Services .................. 197  
J.G. Murray & S.M. Aviso

A 'showcase model' canine rabies prevention and elimination programme:  
the Bohol Rabies Prevention and Elimination Program ...................................................................... 205  
S.M. Lapiz, M.E. Miranda, R. Garcia, L. Daguro, M. Paman, F. Madrinan  
P. Rances, Bohol Rabies Prevention and Elimination Council Members & D. Briggs

Evaluation of various rabies elimination strategies in Latvia ............................................................. 215  
E. Oļševskis, E. Liepiņš, E. Jēgers & K. Lamberga

Recommendations ................................................................................................................................ 223
Foreword

Rabies is a highly significant and fully preventable cause of death in humans and animals. It particularly affects Asia and Africa where insufficient means are available to create the necessary effective immune buffer and protective barrier between the animal source of the disease and the potential mortal victims, the majority of which are caused by rabid dog bites.

Despite considerable advances in novel technologies for the control of rabies and the technical and institutional know-how collected in successful rabies control programmes, rabies will remain to be a threat as long as its control is not adequately tackled at the animal source.

Following the two successful international conferences on rabies, the first held in Kiev in 2005 and the second in Paris in 2007, this third Global Conference, hosted by the World Organisation for Animal Health (OIE) in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), focused on the theme ‘Towards sustainable prevention at the source’ aiming to identify key elements for the sustainable implementation of existing concepts to control rabies at the animal source while also renewing the concepts on inter-sectorial collaboration. The conference also aspired to facilitate the overall vision towards the global elimination of rabies in animals. It is evident that “Controlling the disease in dogs, and especially stray dogs is the first priority in preventing rabies transmission to humans”.

The veterinary profession has a prime responsibility for delivering a service that allows the economically justified control of zoonotic diseases, such as rabies, at the animal source. A combination of measures, including stray dog population management and canine vaccination, is the universally preferred method of controlling and eliminating rabies. To achieve this, the capacity of Veterinary Services and other supporting institutions, both at the national and local levels, needs to be strengthened, together with the communication channels that will allow collaboration among different stakeholders. The conference acknowledged that a rabies control strategy cannot be effective without the support of many different partners coordinated by the authorities, including the animal health services, environmental officers and the police force, and without the support of local and municipal authorities, non-government organizations and dog owners.

Communication, education and awareness programmes are fundamental to achieve rabies control successfully, together with public-private partnerships to ensure sustainability of rabies control strategies.

National governments must take responsibility for rabies control in the animal reservoir, including ensuring transparency in notifying the disease. They should attempt to meet the OIE requirements in making a self-declaration of a rabies-free status for all susceptible domestic and wild animal species. Other areas of discussion included the international movement of pets, pet passports, quarantine, sanitary controls and methods for the monitoring and control of the dog population. The OIE is committed to assist its Member countries in their fight against rabies in collaboration with FAO and WHO as well as the Global Alliance for Rabies Control.

Important highlights of the conference included the development of new diagnostic tools for confirming rabies in animals that could be used in countries throughout the world at a minimal cost and without the need for multifarious equipment. The conference discussed the new developments in animal vaccines, the use of both parenteral and oral vaccination in animals with the complimentary use of immuno-contraception as one of the relevant tools for rabies control in dog populations. The impact of animal rabies on the local economy demonstrated that rabies control programmes are a major financial challenge for many countries as the costs, especially vaccination costs, are very high. Rabies...
control should be considered as an international public good in order to get appropriate financial resources for all nations and all people.

The cost-benefit analysis of rabies control with a focus on the costs for the prevention and treatment of human rabies estimated that about 10% of the financial resources used for post-bite treatment in humans would be sufficient to eliminate rabies at the animal source, in dogs, throughout the world, and so prevent almost all human cases at a minimal cost. Research communities through public-private-partnerships need to work together to manage the cost-effectiveness of vaccine development and to develop vaccines that confer long-term immunity in animals, thereby eliminating the need for booster vaccinations.

It is a societal tragedy that in the 21st century a zoonosis that is a hundred percent preventable in humans and can be easily controlled in its domestic reservoir animal species is still neglected. In moving towards sustainable prevention of rabies at the animal source, I am committed to supporting the efforts of the international community to achieve worldwide elimination of rabies. I am convinced that if those in the veterinary profession work together with their colleagues in the public health and other sectors, we have the ability, knowledge, expertise and commitment to realise my personal vision and the ideal of this conference and to confine rabies in animals to the history books.

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Global perspective of rabies

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Summary

Rabies is a zoonotic disease which affects a number of mammalian hosts, and is caused by a variety of distinct lyssavirus variants. Different variants of rabies viruses and/or rabies-related lyssaviruses occur on all continents, except Antarctica. Each variant is generally associated with a principal host species, whose use of space and social interactions allows the virus to persist in its populations. As there is no single lyssavirus species or variant and no single principal host, there is also no single epidemiological pattern.

Keywords


Epidemiology

Rabies viruses are adapted to the physiological traits and the population biology of their principal hosts. They have a host-specific pathogenicity and pathogenesis. Adaptation of a particular virus variant to its principal host is indicated by the frequency and magnitude of its excretion on one hand, and by the host’s high susceptibility to it on the other hand. These properties allow for transmission from an infective to a susceptible individual in the event of a biting incident. A significant component of how a rabies virus variant spreads through a population is its behaviour in individual hosts. A susceptible animal or human usually becomes infected by receiving a bite from a rabid animal. Rabies has a peculiar pathogenesis, characterised by virus dissemination within nerve fibres, rather than by blood and lymph; rapid expansion of the infection within the central nervous system (CNS), after a variable but generally long incubation period; virus excretion with saliva toward the end of the incubation, and the almost invariably fatal outcome (in the species studied so far). The infection of the CNS leads to behavioural changes that promote infectious contacts. Fox rabies in Europe shall serve here as an example.

After World War II, fox rabies epizootics emerged in North America and Europe. While in North America the spread was predominantly north-south, in Europe it was east-west. The viruses circulating in European and American foxes (Vulpes spp.) are distinct, though both are members of the ‘cosmopolitan branch’ (1). The features of the epizootic expansion in Western Europe have been described and analysed by numerous authors (2, 3, 4). The first rabies cases recorded in newly affected areas were almost always in foxes. The epizootic front advanced in a wavelike fashion, with a speed of approximately 25 km to 60 km per year. The case density in newly affected areas was usually very high (up to 5/km²/year). Rabies in foxes constituted between 60% and 85% of all diagnosed cases in the initial outbreaks. During one outbreak, about 86% of the foxes killed because of abnormal behaviour were rabid, while rabies virus as the aetiologic agent was found in only 60% of abnormal badgers (Meles meles) and 21% of diseased stone martens (Martes foina). Larger rivers,
lakes and high mountain chains functioned as obstacles to the spread. Rivers were usually crossed where bridges were available. Initial outbreaks lasted for about one year.

The epizootic wave leaves behind a largely depopulated area in which the rabies prevalence is very low or nil. Low fox population density, rather than high herd immunity, explains the disease's disappearance. Reduced fox populations recover within two to three years, making them vulnerable to disease re-invasion. The non-synchronous rates of population recovery and disease re-invasion are mirrored by temporal prevalence patterns that vary from location to location. The spatial variation is, in our interpretation, a reflection of habitat conditions dictating varying fox population characteristics (social use of space), though spatial rabies virus variation causing distinct disease patterns cannot be fully discounted. The asynchronous or chaotic prevalence patterns behind the front wave are probably a significant reason for the prolonged persistence of the disease in larger areas. Intensive fox destruction campaigns may have stopped the spread in a few privileged locations. However, it was difficult to reduce fox population densities to levels at which a social transmission network ceased to operate. In contrast, it appeared relatively easy to vaccinate a sufficient proportion of foxes in order to interrupt the disease spread (5), a finding that was predicted intuitively.

Attempts to link epidemiological patterns with fox population parameters have been the primary topic of many attempts to model the virus-host association (6, 7, 8). Rabies transmission is usually thought to be density dependent, though one may easily conceive of scenarios that are density independent. Density dependence can explain the observed prevalence oscillations. Deterministic prevalence models make no attempt to explain spatial dynamics. However, field observations show that rabies epizootics move slowly across the countryside in wave-like fashion, rather than having synchronised incidence undulations over large areas. Field data from well-surveyed areas indicate that the disease invades vulnerable fox populations by transmission from an infected individual to its susceptible neighbour, rather than through regular dispersal movements or disease-induced long-distance travels. Radiotelemetric observation of rabid foxes and the peculiar age and sex distribution patterns suggest the following interpretation. Infected foxes occupy their regular home range during the incubation period. When they become clinically ill, they lose their territorial binding and may venture into their neighbours’ ranges or otherwise provoke a hostile encounter with a nearby resident fox. Adults, and in particular the females, defending their offspring in the summer, are obviously more likely to attack an abnormally behaving intruder, while juveniles or sub-adults may avoid such contacts. This interpretation is supported by the varying age and sex distribution of rabid foxes during the epizootic (9).

Rabies virus variants adapted to different species

Under the influence of the pioneering work of Keith Sikes (10) and Parker and Wilnsack (11) on the high susceptibility of foxes and skunks to the rabies viruses propagated by these species in North America, it was speculated that rabies virus adaptation to its principal hosts is always characterised by high pathogenicity and high levels of virus excretion with saliva. This concept was reinforced by observations on the European fox rabies epizootic. Jean Blancou and his team at the Laboratoire d’études et de recherches sur la rage at la pathologie des animaux sauvages in Nancy, France, established the susceptibility, and the rate and magnitude of virus excretion, for many European species. They found that the red fox has indeed got the highest susceptibility to the European fox virus. However, when inoculated with a North African dog rabies virus, red foxes may develop immunity, rather than disease. Rabid foxes also excrete more virus particles in their saliva than most other rabid animals infected with the European fox virus. From these observations the French team developed the concept of viral biotypes. A particular biotype is a virus variant adapted to a specific principal host species with especially high pathogenicity for this species, a high rate of excretion, and low immunogenicity (12). In addition, the high efficiency of transmission and the high
The reality of rabies: setting the scene

Lethality does not generate any substantial herd immunity in fox populations (9). We might be tempted to view rabies viruses as perfectly adapted to persist in large populations of species with high intrinsic growth rates, that are capable of recovering rapidly after an epizootic wave has reduced the population density to a level at which the reproductive rate of the disease (disease transmission) falls below unity. This appears to fit well with the observation that the Carnivora serving as principal hosts all have similar life history traits and population characteristics. Red foxes, jackals, domestic dogs, striped skunks and raccoons are all opportunistic, medium-sized species with a wide distribution and contiguous populations of relatively high density. Additionally, they all have high reproductive rates that permit rapid population recovery.

High transmissibility and high lethality, as seen in fox rabies in Western Europe, are not indispensable pre-conditions for the continued existence of rabies viruses. The high pathogenicity/high susceptibility, high susceptibility/high excretion, low immunogenicity/low survival triad does not cover all virus adaptations necessary for the survival of a virus in a species with a habitat-dependent population density, turnover and structure, and specific patterns of behaviour and social interactions. A species’ population density and dynamics and the social use of space may vary significantly in different habitats that have different patterns of resource availability and promote different mortality factors.

Rabies virus variants, virus variability and host-specific adaptations

Although most mammalian species are susceptible to infection with rabies viruses, only a few are recognised as important for the persistence of the disease in nature. In these principal host species, a prolonged enzootic existence is possible because of sets of co-adapted traits of susceptibility, viral evasion of immune surveillance, long incubation, excretion in saliva, neurological disorders that promote transmission, host life history traits, social behaviour and population biology. Chiroptera (bats) are identified as hosts of lyssaviruses in Africa, the Americas, Australia, and Eurasia, while bats in the Americas harbour a variety of classical rabies variants. Different species of Carnivora, including the domestic dog, are the principal hosts for rabies viruses in Africa, the Americas, and Eurasia.

The analysis of a very large number of rabies virus variants through partial sequencing of their genomes allows us to perform phylogenetic and phylogeographic analyses (13, 14). These studies confirm that each principal host propagates its distinct virus variant but also demonstrate that mostly silent mutants arise and get established in limited geographical areas through clonal expansion. I suspect that most of these mutants do not convey a fitness change for the virus.

All principal hosts transmit the disease to other species, which are sometimes highly susceptible but whose population biology and behaviour are not conducive to maintaining an epizootic. Genome sequencing confirms that most cases that were interpreted as spillover are indeed victims of exposure to a principal host species. The prevalence of spillover cases in other species is not only a result of their susceptibility, but also of their behavioural peculiarities of exposing themselves to infectious contacts. However, molecular studies also confirm that independent epizootics can co-exist in parallel in different principal hosts, such as distinct variants in different species of bats in the Americas (15, 16) or in different Carnivora in southern Africa (17).

Average frequencies of base substitutions in rhabdoviruses are estimated to be $10^{-4}$ to $4 \times 10^{-4}$ per base incorporated. This level of base change dictates that RNA viruses exist as heterogeneous populations. The expression ‘quasispecies’ is frequently applied to such polymorphic populations. The quasispecies concept suggests the evolutionary potential of genetic variation. A polynucleotide can guide itself along fitness gradients to fitness peaks. However, we are often a bit careless when contemplating adaptive evolution of viruses. If ‘self-guided tours’ in the fitness landscape were an unproblematic option for the rabies virus, one would expect that it should switch principal hosts.
opportunistically. This is obviously not the case; rabies genomes appear to be trapped at local fitness optima. Adaptations to new hosts, or the adoption of other transmission strategies, may both be difficult, due to structural and functional constraints or the need for too many simultaneous co-adapted changes. The valleys between fitness optima may be such constraints as the correlation between incubation and excretion periods with population parameters, viral spread in the host and evasion of immune surveillance. The viral genome must also maintain these properties from the site of entry, through the CNS, to the place of excretion in the salivary glands. Further hindrances to unlimited diversification and adaptive evolution of rabies viruses are the population bottlenecks encountered during the transmission from one individual host to the next and during their spread through neuronal networks in the host. Within this neuronal network, the host viral progeny are transmitted from an infected cell to a small number of susceptible cells. They are not disseminated via lymph or blood to a multitude of different cells, as in most viral infections of vertebrates. The number of genomes that enter a new neuron is not known, but there is no doubt that there are bottlenecks that reduce the chances of mutants becoming established. Mechanisms like Muller’s ratchet (18) may restrict genome variation. Notwithstanding, we must expect future invasions of new hosts at a similar frequency to that at which they have occurred in the past. The colonisation of a new host species is facilitated in particular locations, where habitat conditions instigate a population structure which allows the propagation of a virus variant usually associated with another principal host.

**Wildlife rabies – dog rabies**

In wildlife rabies areas of North America and Europe, only 0.1% to 5.0% of cases reported are in dogs. The spillover of rabies from wildlife into dogs may be a cause for some concern since the majority of virus variants circulating in wild carnivores belong to the cosmopolitan lineage, which is thought to have been spread across the world by dogs accompanying European colonisers (1, 14). So, if some of these wildlife epizootics originated from dog rabies, as recently evidenced in Turkey (19), the reverse might happen as well. Nevertheless, the incidence of dog rabies in the industrialised nations of North America and Europe remains low, due to responsible dog ownership.

This is very different in many African and Asian countries. Over large areas of Asia and Africa, rabies in dogs is much more common, making up 95% or more of all diagnosed cases. The close association of dogs with people allows the opportunity to gather epidemiological information though, regrettably, this is done only rarely. In N’Djamena in Chad (20), the estimated transmission rate between dogs was 0.0807 km²/(dogs·week) and between dogs and humans was 0.0002 km²/(dogs·week). The effective reproductive ratio was estimated to be 1.01, indicating low-level endemic stability of rabies transmission. In Tanzania (21, 22), the investigators estimated incubation periods to average 22.3 days and the infectious periods to average 3.1 days. The mean transmission distance was 0.88 km, though individual rabid dogs travelled much further. The authors also calculated the average number of secondary cases produced by an infected dog, the so-called basic reproductive number \( R_0 \), for the Tanzanian outbreaks, as well as from published information from other parts of the world. The approximate range of \( R_0 \)s is between 1.05 and 1.8. Noteworthy is the statement that the basic reproductive rate of rabies appears to be independent of dog population densities. This is in contrast to the frequent statement that high-density dog populations permit the occurrence of enzootic canine rabies, though it is well known that the disease also persists in dog populations of densities below ten individuals per km².

Latin America is in transition from a high dog rabies prevalence to a significant wildlife rabies prevalence. Efforts coordinated by the Pan American Health Organisation led to successful national and regional dog rabies control programmes, consisting of dog vaccination campaigns, public education, dog population control, and promotion of responsible dog ownership (23, 24).
Human rabies

Wildlife rabies is a significant threat to human health. Rather than wild animals themselves, rabid domestic animals infected by wildlife are the source of exposure for most human cases in the European fox rabies outbreak. This is different in the Americas: in the United States and Canada, most human rabies casualties result from contact with rabid insectivorous bats. This problem is heightened in tropical and subtropical Latin America and the Caribbean Islands, where haematophagous bats transmit the disease to domestic animals (livestock) and humans.

Today, the majority of human rabies casualties occur in Asia and Africa. More than 99% of these cases result from bites by rabid dogs. Dogs are kept and tolerated at very high numbers in most human societies. Dog population densities may reach several thousand per km² (25). This is considerably more than any wild carnivore population ever achieves. In populations of poorly supervised dogs, with a low vaccination coverage, rabies can be a significant problem. Dog bites are frequent. About 1% of the human population experiences dog bites each year in the areas investigated by the author, though most of the bite incidents are not caused by rabid animals.

Worldwide, an estimated 30,000 to 60,000 people die of rabies every year (26). Almost all human rabies deaths, and the vast majority of treatments after bite exposures, occur in developing countries (27). Up to 4 human rabies deaths per 100,000 inhabitants are recorded in some areas (25, 28). This may, in part, be due to a high rate of exposure to biting dogs (29). The highest figures come from South and Southeast Asia, where the annual exposure to dog bites is between 2% and 5% of the population. Not all biting dogs are infected with rabies, and not all bites by rabid dogs lead to clinical rabies in the bite victim. The reality that a dog bite only rarely leads to a death from rabies makes the dog-bite syndrome vulnerable to ‘successful’ intervention by all kinds of healers (25). Ignorance about the urgency of obtaining the proper post-exposure prophylaxis in time, the effort of travelling multiple times to a treatment centre, and the easy availability of traditional prevention methods contribute to the relatively frequent occurrence of a lethal disease that is completely preventable.

Rabies control programmes aim to protect human health and prevent economic losses. The occurrence of rabies in humans can be inhibited by pre- and post-exposure prophylaxis and by reducing the risk of exposure, or, conclusively, by disease elimination in the host species. The easiest way to reduce the incidence of human infection is by prophylactic immunisation of those domestic animals which are the most common source of human exposure. It is a considerably more ambitious task to eliminate rabies in its principal host populations. Recent successes in dog and wildlife rabies control should encourage us to increase our efforts. Nevertheless, this must not distract us from educating people on good dog-keeping practices, bite avoidance, bite treatment and post-exposure prophylaxis, which should be available to everyone who needs it.

Conclusions

Rabies is caused by a plethora of lyssaviruses, of which the classical rabies virus is the most important in domestic or wild animals. As there is no single lyssavirus species or variant and no single principal host, there is also no single epidemiological pattern. Different virus-variant-host associations are of differing importance to human health. Although this disease is entirely preventable, no substantial progress has been made in eliminating rabies on a global level at the beginning of the 21st Century. As a neglected disease, canine rabies causes tens of thousands of human deaths per year, especially in developing countries. Nevertheless, a few important steps forward have been achieved. Rabies in several species of wild Carnivora has been successfully eliminated from relatively large areas of Europe and North America through oral immunisation of the principal hosts. It is also quite obvious that dog rabies can be brought under control if there is a political will to do so.
**Recommendations**

As different classical rabies virus variants are maintained by different animal host species, eliminating rabies is possible by targeting control strategies in the reservoir host alone. Though this statement is valid for dogs and many wild *Carnivora*, no such claim can be made for the numerous rabies virus variants circulating in different bat species in the Americas. It is essential that all rabies control programmes and strategies should be considered both in their veterinary and in their medical context. Rabies could serve as a practical approach and ‘hands-on’ example to facilitate the application and accelerating the necessary leverage of ‘One Health’.

**References**


Towards sustainable prevention of rabies at the source: a case report from India

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Summary

Elimination of canine rabies constitutes the most effective means of controlling human rabies and avoiding expenses associated with prevention programmes, which could be better used for other public health priorities in the developing countries of the world, such as India. The World Health Organization sponsored a multicentric study of rabies in India between 1993 and 2002 and showed that the incidence of human rabies cases in India remained more or less steady during this period, at about 17,000 cases per year. Human rabies is endemic throughout the mainland of India and only the islands of Andaman and Nicobar and Lakshadweep are rabies-free. The majority of human rabies deaths occur in poor/low-income groups. The average annual incidence of human rabies deaths is estimated at 17,137 (14,109 to 20,165, with 95% confidence). In addition, workers report an atypical form of rabies in 20% of cases, which brings the total to 20,000 deaths every year. The principal animal reservoir is the dog (96.3%). The companion dog-to-human ratio is estimated to be 1:36 and the frequency of human deaths is calculated at 1 every 30 minutes. The most common animal reservoirs of rabies, based on laboratory evidence, are dogs, cattle, goats, cats and pigs and, among wild animals, the mongoose and the jackal. Dogs continue to be the main source of human rabies infections. It is calculated that 97% of human rabies deaths are from the bites of rabid dogs, with children being the most commonly affected.

Keywords

Introduction

Epidemiological situation of rabies in India

There have been no systematic studies on the incidence of rabies in animals in India and the reported incidence is taken from the annual reports of State Departments of Veterinary Services to the Department of Animal Husbandry, Government of India. Post-mortem records maintained in the pathology departments of veterinary colleges are the most reliable source of canine rabies deaths (1, 2).

It has been estimated that nearly 96% of people seeking anti-rabies treatment were exposed to dog bites. The increase in the dog population has resulted in an increased incidence of dog-bite cases. There has also been an increase in the incidence of rabies in cattle, sheep, goats, horses and cats as evidenced by post-mortem reports from various veterinary colleges across the country (5).
The reporting system for canine rabies is far from satisfactory. There is no coordination between the various agencies responsible for control programmes and, as a result, the authenticity of the data available on the incidence of rabies in the country is doubtful.

**Table I**

*Animal rabies deaths reported in India in 2009*

<table>
<thead>
<tr>
<th>Rabies</th>
<th>Outbreaks</th>
<th>Attacks</th>
<th>Deaths</th>
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<td>Bovines</td>
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<tr>
<td>Total</td>
<td>97</td>
<td>324</td>
<td>324</td>
</tr>
</tbody>
</table>

In addition, no systematic survey of the dog population has been undertaken but unconfirmed reports place the companion dog population at around 25 million, with 28 million stray dogs. It is also reported that, every year, 17.4 million dog bites are reported, of which only 3 million receive post-exposure vaccination. The frequency of bites is estimated to be 1 bite every 2 seconds. The use of rabies vaccines in India is very low and that of rabies immunoglobulins negligible (7).

In this report, two examples of the prevalence of rabies in animals are examined; one from the Veterinary College, Bangalore, and the second from the Veterinary College, Chennai. In both cities, the incidence is higher in dogs than in any other animals (Figs 1 and 2) (5).
Discussion

Organisations and agencies involved in rabies control in India

There are two types of organisations and agencies which are involved in rabies control in India, namely: government agencies and non-governmental agencies.

Government agencies

Government agencies include:

- the Ministry of Health – Central and State
- the Ministry of Agriculture – Central and State
- the State Animal Husbandry Department
- the Animal Welfare Board
- local civic bodies
- the National Institute of Mental Health and Neurosciences, Bangalore
- Government Veterinary Colleges, Government of India.

Various projects on both human and animal rabies prevention are being implemented by these agencies.

A pilot project on the prevention and control of human rabies has been initiated by the National Institute of Communicable Diseases, Ministry of Health, and is being implemented in five cities; namely: Ahmadabad, Bangalore, Delhi, Pune and Madurai. This project, which was started in 2008, has been extended to 2012.
The strategy of the project is to: enhance general awareness of timely and appropriate post-exposure treatment, train health professionals, ensure the availability of vaccines and anti-sera, offer the intradermal route of vaccination in selected centres, strengthen diagnostic capabilities and establish an interface with the Animal Husbandry Department.

**Involvement of non-governmental agencies and the community**

There are many non-governmental agencies (NGOs) involved in rabies control in India and predominant among them are the Association for Prevention and Control of Rabies in India (APCRI) and the Rabies in Asia Foundation (RIA). In addition, international organisations, such as the Global Alliance for Rabies Control (GARC) and the Commonwealth Veterinary Association (CVA) are playing an important role in control programmes.

Many projects have been initiated by these organisations, including an NGOs’ Village Adoption Project, to create awareness of rabies and include an introduction to rabies in the school curriculum, with the aim of increasing knowledge about rabies among schoolchildren.

**The ‘Adopt-a-Village Programme’ for rabies control In India**

Ten villages surrounding Bangalore and Pune, India, will benefit from a programme aimed at reducing the incidence of human and animal rabies through improved educational awareness and mass vaccination of dogs.

A large number of medical and veterinary partners are working together in the target villages to educate people in their own language, while being sensitive to their customs. The Karuna Animal Welfare Association of Karnataka, Bangalore, is also involved in the activity. Restricted/supervised pet dogs and strays are collared, vaccinated against rabies and dewormed.

In addition, hands-on training in rabies diagnosis has been given to medical and veterinary personnel, using the direct rapid immunohistochemical test.

**Pilot education project in Karnataka State**

To relieve the burden of rabies in animal populations in India, especially in dogs, and eliminate human rabies deaths, a project has been developed, based on the premise that children are the best target audience to adopt the concept of responsible pet ownership. Furthermore, up to 60% of all people who die of rabies are children (7). This project aims to introduce the topic of rabies into the school curriculum and to educate children about the disease.

Target beneficiaries of this project will include 54,529 primary schools with 252,875 teachers and 8.495 million students, and 9,498 secondary schools with 92,287 teachers and 1.384 million students. The goal is the incorporation of rabies education into 54,529 primary schools by 2013 and 9,498 secondary schools in Karnataka State by 2015.

**Project on evaluation of the neutralising activity monoclonal antibody combination against rabies**

For reasons of safety and availability, alternative products to human rabies immunoglobulin and equine rabies immunoglobulin are advocated, and the development of rabies-virus-specific monoclonal antibodies has been recommended by the World Health Organization (WHO) (www.who.org). Genotypic characterisation of the rabies virus from various geographical locations in India will be undertaken and the aim of the project will be to provide an alternative therapy to rabies immunoglobulins by developing a human monoclonal antibody cocktail’ for post-exposure prophylaxis.
Animal birth control programmes

There has been a very effective animal birth control (ABC) programme in India, which follows guidelines from the Animal Welfare Board of India. Programmes like this have been initiated in many cities in India and there are very good examples from Jaipur and Chennai of how the incidence of rabies has been drastically reduced by a combination of dog population control and rabies vaccinations (Figs 3 and 4) (6).

**Fig. 3**
Animal birth control programme to reduce the number of human rabies deaths in Chennai

**Fig. 4**
Animal birth control programme to reduce the number of human rabies deaths in Jaipur
Dog-catching vehicles, each with trained dog catchers, are deployed to catch dogs. On average, 1,800 stray dogs per month are caught and immunised in the cities of Chennai and Jaipur (4). However, there are many challenges in the implementation of this programme, which include:

- accessing dogs
- sustainability
- cost effectiveness.

At the same time, solid waste management needs to be addressed, as the presence of garbage on the streets is a contributing factor to the huge number of strays in India.

**World Rabies Day programmes**

During the last few years, observing World Rabies Day on 28 September every year has played a very important role in increasing awareness about rabies. Various programmes have been undertaken each year, such as road shows, rallies and education campaigns, involving the media and celebrities such as film stars and sportspeople, especially cricketers, since cricket is such a popular sport in India.

**Challenges for rabies control in India**

There are many key issues which need to be addressed, including:

- the fact that rabies is not considered a priority disease in either animals or humans
- inadequate data and information
- lack of political support
- lack of consensus on strategy
- lack of responsible dog ownership
- weak coordination among the various sectors
- inadequate management structure
- lack of public cooperation.

In addition, limited surveillance data, gaps in surveillance standardisation across reporting departments and poor coordination between departments, along with an absence of the ABC against rabies programme in rural areas and the limited role played by the Animal Husbandry Department, are key impediments to rabies prevention and control in India.

Those surveillance data that are available, both for humans and animals, do not allow definitive comment on the impact of various interventions for the prevention and control of rabies. Generating the political awareness and will for a large-scale control programme is another major challenge and no sector has taken ownership for dog rabies control.

There is a great need for the development and implementation of a national rabies control strategy and for devolving responsibility to local government authorities. Enforcement of the existing legislation on registration/licensing and vaccination of dogs and a strong action plan to control rabies at the source are also urgent requirements in India.
Conclusions

Considerations for rabies control in India

General considerations

To prevent rabies, the introduction of cost-effective public health intervention techniques to improve accessibility, affordability and availability of post-exposure prophylaxis is necessary. In addition, we need to:

- improve our understanding of rabies through advocacy, awareness, education and operational research;
- provide coordinated support for an anti-rabies campaign, with the involvement of community, civil society, government and non-government sectors and international partners;
- establish surveillance for humans as well as animals, and identify rabies as a notifiable disease;
- strengthen State-level coordination committees;
- identify and fill in the gaps in current anti-rabies programmes, e.g. rural and peri-urban areas pose a major threat to the success of rabies control efforts;
- document rabies interventions as a model for replication;
- draft a blueprint that can guide the national disease control programme in combating rabies and other zoonoses in the country;
- strengthen the available laboratory facilities for rabies diagnosis in animals and humans.

Specific considerations

The following considerations should also be taken into account:

- human rabies prevention is possible through the promotion of responsible dog ownership, mass dog vaccination and animal birth control programmes with a partnership approach;
- mass vaccination campaigns targeting dogs of all age groups should be undertaken to develop herd immunity;
- mass dog vaccination alone is effective but providing additional dog population management interventions can help overcome the challenges involved;
- world Organisation for Animal Health (OIE) recommendations and standards should be adopted and implemented;
- rabies should be considered a priority by all governments;
- there is a need to increase public awareness and education on rabies;
- Veterinary Services can make an active contribution to the goal of eliminating human rabies at the animal source, with the appropriate financial support (public budget/Ministries of Health);
- comprehensive and sustainable national programmes for rabies elimination must be designed and implemented;
- we further need to harmonise control and elimination programme strategies between neighbouring countries until rabies has been successfully eliminated.
References


Rabies in China

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Summary

Since the late 1990s, the country reporting the second-highest number of human rabies deaths worldwide has been the People’s Republic of China. The disease is predominantly distributed in southern China with more than 85% of human rabies cases occurring in rural areas. This review outlines the current situation and the control strategy for rabies in China with a focus on epidemiology, animal vectors, viral evolution, control programmes and accompanying measures. It also examines major challenges and future plans for controlling rabies at the animal source.

Keywords


Results

Epidemiology

Rabies is a zoonotic disease, causing severe damage to the central nervous system, with almost all cases being fatal. Animal rabies is distributed worldwide, but human rabies is largely restricted to Asia and Africa (9). In the People’s Republic of China, rabies is one of the most severe public health problems and, in fact, China has been the country reporting the second-highest number of human rabies deaths worldwide since the late 1990s (8). According to the Ministry of Health of the People’s Republic of China (MoH), about 40 million people in the country are injured by dogs and cats every year (5). The latest epidemic wave of human rabies started in 1997 with 222 cases, reaching its peak in 2007 with 3,303 cases (Fig. 1). This rapid increase was accompanied by an expansive increase in the number of rabies-endemic regions, with 120 counties reporting cases in 1999, and 984 in 2007 (i.e. 34.3% of the total number of counties in China). Currently, 23 of the 31 provinces, autonomous regions and municipalities have reported human rabies cases (5).

With the implementation of comprehensive control measures by the government in 2005, the number of reported human rabies deaths has been significantly declining, with 2,378 cases in 2008; 2,108 in 2009; 1,988 in 2010 and 1,896 in 2011 (4). This reduction indicates that the control strategy continues to be effective. It consists of compulsory registration and vaccination of companion dogs in urban districts, the gradual implementation of mass vaccination of rural dogs, the increased availability of post-exposure prophylaxis (PEP) to people injured by dogs, particularly in rural areas; education programmes to raise awareness, and improvement of medical and veterinary infrastructures.
The reality of rabies: setting the scene

Fig. 1
Human rabies deaths in China from 1950 to 2010

Human rabies is predominantly distributed in southern China with comparatively few cases in the north, largely as a result of demographics (Fig. 2). The dog-to-human ratio in southern China (with at least one dog per rural family) is substantially greater than in the north and the potential risk of exposure to a rabid dog is therefore greater. Five north-western provinces reported seven human cases during the last ten years, and three north-eastern provinces reported 11 human cases, compared to more than 1,000 human rabies cases reported every year in the southern provinces, Elsewhere, Hong Kong, Macao and Chinese Taipei have remained free of human rabies cases. Epidemiological studies have shown that more than 85% of human rabies cases came from rural areas, with an incidence in men of up to 2.5 times that in women. Children and young adults accounted for 68.6% of the total. These data are consistent with what is known about human rabies in other developing regions of the world. In all of these countries, rabies is recognised as a disease of poor rural communities, of the under-privileged and, principally, of the young (8).

Fig. 2
The occurrence of human rabies cases in China, by location, in 2007
In China, the dog plays a pivotal role in rabies transmission, with more than 95% of human cases ascribed to dog bites (mostly rural rather than companion animals). Of the remaining cases, 3% are due to cat bites and 2% to contact with other animal species (8). Ferret badger-transmitted human rabies cases have been reported recently (2), with the rabies virus being detected in, and isolated from, these animals (*Melogale moschata*) (11). A bat-associated human rabies case was reported in 2002 and another in 2010, but no laboratory confirmation was made with either patients or bats. One human rabies case was reported to have been caused by the bite of a rabid pig in Zhejiang Province in 2007 (Chengxing Han, unpublished data).

**Discussion**

Since dogs in rural areas do not require registration in China, the size of the population is difficult to estimate precisely. Dog demographics depend largely on culture and geography, and numbers differ substantially in different regions of China. A dog census conducted in 2007 by the Chinese Centre for Animal Disease Control and Prevention (CADC) estimated that China had about 75 million dogs, with most in rural areas (5). Rural dogs are usually raised to guard the house and sometimes for consumption. They are aggressive and left free to roam, thereby not only increasing the risk of human exposure to dog bites but also making data collection difficult, in contrast to the situation in cities where most dogs are registered as companion animals.

The current situation of animal rabies in China is not well understood, due to insufficient surveillance and limited awareness of reporting and compiling statistics on animal rabies cases. The available data show that, in addition to the wide prevalence of dog rabies, the disease has also been reported in such animals as a cow (1), buffalo (10), pigs (3), sheep (12), sika deer (6), ferret badgers (11) and raccoon dogs (7). At present, there is no scientific evidence for infection by, or circulation of, other lyssaviruses in China. Whether or not other wild carnivores are naturally infected with rabies viruses is unknown, since the relevant studies and surveillance of wild animals have not been undertaken.

Based on phylogenetic analyses, rabies virus isolates from China have a close relationship with those from Southeast Asia and are divided into three major groups (1). The Chinese isolates, however, are not closely related to the isolates from South and Central Asia.

**Control**

Facilities for PEP treatment and sufficient vaccine supplies are readily accessible in most cities and counties for patients who have experienced dog bites. Moreover, 15 regions of provinces where rabies is highly endemic have been selected as national rabies surveillance spots by the national rabies surveillance programme, established by the Chinese Centre for Disease Control (CDC) in 2005. This surveillance includes case examinations, PEP investigation, laboratory diagnosis and molecular epidemiological studies of the rabies isolates.

The Ministry of Agriculture of the People’s Republic of China (MoA) initiated an annual Rabies Immunisation and Surveillance Programme in 2005 to improve control of dog rabies, particularly in rural areas. In 2008, the MoA announced a regulation requiring full vaccination of all types of dogs throughout the country. The vaccinated dogs are usually labelled with ear tags (rural areas) or biochips (some urban areas).

In urban areas, a well-established dog registration and vaccination programme is in place at the owner’s expense, ensuring adequate immunisation coverage of urban dogs. In these areas indigenous rabies rarely occurs. However, in rural areas, dog vaccination is not widely accepted due to poor awareness and the high cost of vaccine administration. The central government does not provide a special budget for dog vaccination and immunisation coverage is highly dependent on the economic
status of the local government. Most of the latter have insufficient budgets to support vaccination, and therefore immunisation coverage is only 10% to 20% in most rural areas (5). Only a few developed provinces and big cities have established a steady budget to support the vaccination of all urban and rural dogs. In these areas, the relatively high immunisation coverage has resulted in a substantial decline in human rabies cases, even resulting in the complete absence of cases during certain years.

The dog is the only animal species in China subjected to anti-rabies vaccination and animals of other species are rarely vaccinated. Two types of modified live vaccines are licensed and produced in the country. One is made from strain Flury LEP, and is widely used for rural dogs at government expense. The other is based on strain ERA, formulated in combination with canine distemper, canine adenovirus, parvovirus and para-influenza virus vaccines. This combined vaccine is used mainly in urban dogs at the owner’s expense. In addition, four imported killed vaccines have been approved for use in China. Since they are very expensive, these vaccines are mainly administered in urban dogs at the owner’s expense, with only a limited quantity used in rural dogs at local government expense.

A national diagnostic laboratory for animal rabies was established in the Changchun Veterinary Research Institute, which was authorised by the MoA in 2005. In addition, several provincial CADCs have established their own laboratory capability to deal with the worsening rabies situation through diagnosis and surveillance. Increasing numbers of diagnostic laboratories at provincial CADCs are joining to form a national network of veterinary laboratories for rabies diagnosis. This will strengthen diagnosis and surveillance with the focus on suspected rabid animals.

Conclusions

Major challenges

Most provincial and municipal governments have implemented local legislations or regulation to reinforce dog management and rabies control, but relevant legislation at the national level still does not exist. In China, the registration and management of rural dogs is still a great challenge, which significantly affects the implementation of vaccination programmes in rural areas.

To apply comprehensive control measures, close liaisons between related government sectors need to be strengthened. Compulsory vaccination of dogs against rabies should be mandated through legislation and implemented throughout the country more effectively than at present.

Owing to a lack of awareness, cases of animal rabies are not always reported to the relevant veterinary administration, leading to an underestimation of the true rabies situation in animals. Only several hundred animal rabies cases are reported to the national CADC annually, much lower than the number of human cases reported to the national CDC. The majority of animal rabies cases are not confirmed by laboratory diagnosis, so active reporting and collection of any suspect animals should be encouraged, especially by the various levels of the Veterinary Services. The public should be educated and encouraged to report suspected rabid animals immediately, to the local Veterinary or Medical Services, to reduce the potential for onward transmission of rabies from the suspect animal.

Stray dogs and cats are becoming increasingly large public health problems in a number of cities and towns, since neither disease control measures nor adoption protocols exist. Systems should be established for adoption and euthanasia and, to control the size of dog and cat populations, neutering or contraceptive measures should also be considered to restrict random breeding of the animals.

In rural areas, particularly in undeveloped and remote regions, the accessibility of PEP should be improved. Most human rabies cases do not receive a PEP regimen and in rural areas many people
injured by dogs do not receive PEP (5). The reasons for this include inaccessible vaccine and rabies immunoglobulin, and a lack of awareness of the availability of or need for prophylaxis. Consequently, the education of the public about rabies exposure and rabies control should be intensified.

**Recommendations**

**Future plans to control rabies at the source**

The MoA has initiated a long-term (2011 to 2020) animal rabies control plan, in cooperation with the MoH. This plan aims to significantly reduce the incidence of human rabies by the implementation of a comprehensive dog rabies control strategy, the main goal of which will be to achieve 70% dog vaccination coverage.

Killed vaccines developed by different institutes and biological companies using different fixed strains of rabies virus were registered and licensed by China last year, and these will be marketed to replace the currently used live vaccines. Several novel genetically engineered vaccines are also under development and have shown promising results.

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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
The reality of rabies: setting the scene

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

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 (*R₀*) at which the social networks of the animals ceased to operate and transmission was interrupted (*R₀ < 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]).

![Assumed spread of the fox rabies epidemic in Europe during the 20th Century](image)

**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.
Acknowledgements

The elimination of terrestrial rabies from large parts of Europe would have been impossible without the constant motivation, continuous commitment and untiring efforts, even passion, of the various Veterinary Authorities and hunters’ associations of all those European countries who have implemented ORV programmes, as well as the support of OIE, WHO and all other stakeholders. The efforts of scientists and their staff in developing oral rabies vaccines and adequate surveillance and vaccination strategies, as well as all those national and regional veterinary laboratories who have tested scores of samples in the course of routine rabies diagnosis and monitoring ORV campaigns over the past 30 years, also deserve our great appreciation.

References


Epidemiological factors and control of rabies in North Africa

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Summary

The North African region extends from the Mediterranean Sea in the north to the Grand Sahara in the south; the Atlantic Ocean to the west and Egypt to the east. The total area is around 4 million km² and encompasses four countries: Morocco, Algeria, Tunisia and Libya. There are approximately 90 million inhabitants and 45% of them are rural. The livestock population is close to 70 million large animals and the dog population is estimated at four to five million.

Rabies is a serious public health concern in North Africa, creating a heavy social and economic burden. Its reintroduction represents a threat to Western European countries that are currently free of canine and vulpine rabies, but which continue to identify some human and animal cases, mostly imported from North Africa. Rabies is a reportable disease in North African countries and specific legislation is in place for disease notification and control measures.

The objective of this presentation is to take a global, multidisciplinary approach to draw a precise picture of rabies epidemiology in North Africa, by identifying the key factors for rabies dynamics, and to provide recommendations for prevention and control strategies. All data are provided by the RabMedControl project, funded by the European Union.

Keywords


Introduction

Animal rabies in North Africa

Animal rabies presents a significant public health problem in Algeria, despite the establishment of a national committee for rabies control in 1984. The disease is endemic with a seasonal peak in spring; around 950 cases are reported yearly. The most affected regions are in the centre of the country and coastal areas. The south is currently free of rabies. Dogs are the main reservoir of the disease with an average prevalence of about 50% of the reported cases. Cattle remain the main livestock victim of the disease, after dogs (3, 6).

In Morocco, the disease is endemic with an average of 409 reported animal cases per year. In general, the evolution curve of human rabies follows that of animal rabies. All provinces are affected to varying degrees, except the southern desert (7). Dogs are the source of all contamination, but ruminants are the main livestock victims (Fig. 1).
The rabies situation in Tunisia is similar to that in other North African countries, with about 200 cases notified yearly; 70% of these are rabid dogs (4) (Fig. 2). No data are available from Libya.

To summarise, the epidemiological situation of rabies in North Africa demonstrates the following specific characteristics:

- dogs remain the main reservoir and transmitter of rabies (40% to 70% of notified cases)
- 85% of cases come from rural areas
- among livestock species, ruminants (19% to 39%) and equines (6% to 19%) are the main victims of rabies
- the southern desert provinces are free from rabies.

![Fig. 1](image1)

**Fig. 1**
Evolution of animal rabies in Morocco (notified cases per year, 2001–2008)

![Fig. 2](image2)

**Fig. 2**
Human rabies in North Africa

On average, 22 human fatalities are reported each year in Morocco and Algeria (ranging between 12 and 35), and one to three per year in Tunisia (3, 5, 7). Some 86% of these fatalities are unvaccinated and 14% have their post-exposure prophylaxis (PEP) interrupted. Children remain the principal victims of canine rabies (56%), while 89% of reported cases in North Africa are due to dog bites of mostly unknown origin (7).

Around 200,000 people a year receive PEP treatment after a potential rabies exposure in North Africa. There are around 120 PEP centres in Morocco, with an average PEP treatment costing $90 per person. The treatment costs are entirely borne by governments and thus global human rabies prevention is a huge cost to North African countries (7).

Results

Phylogeny of rabies isolates

The phylogeny of rabies isolates collected from the North and Sahel regions of Africa show (8):
– a strong spatial segregation of the circulating isolates, with no exchange between North Africa and the Sahel region
– limited diffusion from one country to another
– limited movements between Algeria and Morocco
– a clear subdivision of strains between countries
– evidence that the periodic reintroduction of the rabies virus to Europe is mainly due to the illegal importation of dogs from North Africa.

Discussion

Control strategy

In Algeria, a long-term programme was initiated in 1996, based mainly on three actions:
– the reduction of stray animal populations
– vaccination of domestic carnivores
– vaccination of cattle (since 2003).

Vaccination coverage is estimated at 10% of the dog population (6).

In Tunisia, the control strategy is based on two components:
– vaccination
– stray dog population control.

Vaccination coverage in Tunisia can be estimated at approximately 48% of the dog population (4).

A control programme was initiated in Morocco in 1986, and modified in 2001. The programme is based on dog vaccination and the elimination of stray dogs. An average of 300,000 dogs are vaccinated each year and 30,000 eliminated (7). Vaccination coverage is estimated at 25% of the dog population (Fig. 3).
Limitations of rabies control programmes

The implementation of various control programmes in North Africa shows that the vaccination coverage established in the dog population is not high enough to break the transmission cycle of the disease. Various factors could be responsible for this, such as:

- a deficiency in public education about rabies, causing insufficient participation from dog owners
- insufficient knowledge of the dynamics of canine populations
- inadequate coordination between the departments involved, due to a lack of clearly defined responsibilities.

Table I
Estimates of the density of the dog population in North Africa, with the dog ratio per household (1, 2, 9)

<table>
<thead>
<tr>
<th>Country</th>
<th>Dog ratio per household</th>
<th>Total estimated dog population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban population</td>
<td>Rural population</td>
</tr>
<tr>
<td>Morocco</td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Algeria</td>
<td>1.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Egypt</td>
<td>–</td>
<td>5.9</td>
</tr>
</tbody>
</table>

This dog population is characterised by high mortality during the first year, which makes the population very young (2 to 3 years old), with 62% coming from rural areas and the majority being males (60% to 78%). The characterisation of stray dog populations is necessary for any vaccination programme.

As a consequence, this high turnover rate of the dog population may require at least one vaccination campaign per year.
**Conclusions and recommendations**

Despite substantial and committed efforts, rabies is still endemic in North African countries and far from being under control. This disease continues to cause human fatalities and hundreds of animal cases. The author suggests that:

- a dynamic canine population (with an estimated turnover rate of 30%), leading to insufficient vaccination coverage, indicates that at least one vaccination campaign per year should be targeted at dogs

- ecological factors involving dogs and the impact of human socio-cultural perturbations and human behaviour may play a role in rabies dynamics and vaccination efficiency.

**References**

Rabies and rabies control in African regions

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Summary

Despite the preventability of rabies, the disease has progressively expanded in dog and other carnivore populations of sub-Saharan Africa over recent decades. Although rabies is a notifiable disease in the majority of African countries, it is easily neglected as it often oscillates in a disconnected fashion between authorities concerned with either human or animal health. Given a disconcerting lack of epidemiological surveillance and inconsistent reporting to regional and global structures, the objective of eradication will always be difficult to justify on national agendas or to global funding agencies.

On a continental level, the One Health approach has already been shown to be successful for dog rabies control in at least one part of the developing world, when implemented by the Pan American Health Organization in Latin America. In contrast, there is no pan-African approach to rabies control, although small regional efforts present hope. The rabies control programme in Kwa-Zulu Natal (KZN) in South Africa, supported by the Bill and Melinda Gates Foundation, celebrated a year free of human rabies on 24 June 2011. That occasion constituted the first time in 20 years that KZN has not recorded a single human death from rabies in a full calendar year. This is, however, a very small victory in the face of the continent-wide challenge. The authors suggest that the road to an effective strategy for rabies control in Africa starts with a pan-African approach towards establishing sound surveillance and reporting structures. Clearly, only a sustained and reliable demonstration of the extent of the disease burden will allow a higher priority to be given to rabies on national and global agendas. The success of such a venture is certain to be conditional on the coordinated guidance and support of the World Organisation for Animal Health, the World Health Organization and other global partners in the ‘One Health’ model.

Keywords

Introduction – a brief history of rabies in Africa

In contrast to the situation in Europe and Asia, the introduction of canine rabies into most of Africa is thought to have occurred in recent decades. At present, the disease is still expanding into new hosts and into new geographical niches on the vast African continent. Although rabies in northern Africa is thought to have been present before the emergence and dissemination of the current known ‘cosmopolitan’ strain of rabies virus (13), the manifestation of dog rabies in southern Africa corresponds with, and is associated with, 20th Century European colonialism in Africa. The introduction of canine rabies into East Africa notably led to numerous outbreaks and new epidemiological cycles in several different (and new) host species. From East Africa, canine rabies spread southwards and westwards across borders to neighbouring countries, reaching Zambia in southern Africa by 1913. From here, canine rabies continued with a south-westerly pattern of spread into Angola, Botswana, Namibia and finally South Africa, where it has been confirmed in wild and domestic canids since the 1950s. Although Namibia and South Africa had reported rabies as early as 1887, the disease was associated with herpestids. It is the virus strains associated with canines that caused the rapid spread of rabies in sub-Saharan Africa and which are now responsible for the majority of human and animal rabies deaths (13).

The emergence of dog rabies in sub-Saharan Africa led to infections of multiple species of wildlife, some highly endangered, such as the African wild dog (Lycaon pictus), which further threatened these species with extinction (4). Other seriously affected species include the greater kudu (Tragelaphus strepsiceros) in Namibia (10), wolves (Canis simensis) in Ethiopia (14) and the black-backed jackal (Canis mesomelas) in southern Africa (20). The black-backed jackal has become a key player in rabies maintenance and distribution, as this species is distributed from South Africa to Sudan, occurs in high densities, and is known to interact with a wide variety of other species, including dogs (8). It may well be that the black-backed jackal could, as a rabies vector, become comparable to the red fox of Europe and the raccoon of North America, if dog rabies in Africa follows the same course as the present-day scenario in these developed regions of the world. Indeed, jackals have been identified as the source of rabies in bat-eared foxes in South Africa (15), as well as in kudu antelope in Namibia (10). The Namibian epidemic of kudu rabies, with evidence for a newly evolved independent cycle of rabies in this ruminant species, is, by all accounts, unique (16).

Canine rabies in Africa

As elsewhere in the developing world, it is the presence, maintenance and spread of rabies in domestic dogs that is most important from the human health, disease burden and cost perspectives (7). Irrespective of various arguments for surveillance bias, rabies is most commonly diagnosed in dogs throughout Africa, as exemplified in the Southern African Development Community (SADC) Animal Health Yearbook for 2010 – which listed dogs and cats (63%), followed by cattle (18%), as the most common animal species diagnosed with rabies in 2009 (17). Estimates for rabies on the African continent place 634 million people at risk from endemic canine rabies, with predictions of 24,000 human deaths per annum (5). It is precisely in this regard that a significant conundrum emerges for the African continent. There is a major disconnect between predicted/estimated rabies cases and those rabies cases that are officially reported. This disconnect is true for the entire developing world, but arguably most severe in the case of Africa. Misdiagnosis has also been reported as a factor in the underestimation of human rabies (2, 9). Present-day Africa is highly diversified, with many unstable and extremely poor nations (Africa is the world’s poorest continent). Apart from poverty and the sheer size and harshness of much of the land, there are significant language barriers across the African continent. It is no surprise, therefore, that there is no pan-African approach to rabies control.
Southern and Eastern African Rabies Group

It is from the perspective of the lack of a pan-African rabies control approach that the Southern and Eastern African Rabies Group (SEARG) has operated from the early 1990s. Briefly, the Southern African Rabies Group (SARG) was founded at a gathering of rabies scientists, diagnosticians and policy-makers in Lusaka, Zambia, in 1992. This gathering met under the leadership of Arthur King (Veterinary Laboratories Agency, Weybridge, UK) and the group aimed to establish the true extent of rabies in the ten countries that attended the first meeting. In 1993, SARG became the Southern and Eastern African Rabies Group (SEARG). Since then SEARG has grown, with 18 African countries attending the tenth SEARG meeting.

While the original idea was to create a rabies platform for the Anglophone countries of Africa (hence, primarily countries from the southern and eastern parts of the continent), SEARG now aims to incorporate new African countries as a step towards the establishment of an inclusive African Rabies Group (rather than just southern and eastern countries). One collaborating group in this regard has been the African Rabies Expert Bureau (AfroREB), a group focused on human rabies in Francophone areas of Africa, under the auspices of the pharmaceutical company, Sanofi Pasteur (3). A further objective would be to facilitate the involvement of more African countries in the activities of the United Nations' World Rabies Day and to liaise with any other rabies interest groups on the continent.

The overall objectives of SEARG have remained virtually unchanged since its inception and include the following:

(i) to engage the different countries in the group and assist their rabies control policies to evolve, taking into account the latest information and technology on the disease
(ii) to encourage Members to conduct adaptive research and employ rabies control strategies used successfully in other parts of the world
(iii) to solicit funds to be used in conducting rabies control/eradication projects
(iv) to critically analyse rabies control/elimination programmes in the southern and eastern African regions and come up with innovative ways of improving such programmes
(v) to encourage dialogue between all scientists working on rabies, especially between medical and veterinary scientists
(vi) to provide technical training and assistance to its Members (www.searg.info/).

Over time, and through regular open international meetings, SEARG has been successful in facilitating extended international liaison and cooperation, involving African states and the main international reference and collaborative centres.

In recent years, SEARG has attempted to focus on the problem described above – i.e. the gap between global predictions and actual reports of rabies cases from Africa. For example, one of the resolutions of the 2008 SEARG meeting in Botswana was to increase rabies diagnostics and surveillance training initiatives for countries in the SEARG region. African scientists are often confronted with limited institutional commitment and support and a general lack of awareness for zoonotic pathogens such as rabies. In this regard, we believe that SEARG presents an opportunity to make a difference by improving efforts to better profile and control this important, yet neglected, zoonosis.

Since the founding of SEARG, several issues have been raised to try to improve rabies surveillance and control across Africa. Some of these issues have been addressed by SEARG; however, there have also been a number of issues that continue to be voiced without any specific action. These issues reflect the successes and the shortcomings of the SEARG group as a whole.
An important issue that has been raised at several SEARG meetings (1992, 1993, 1995 and 2008) has been the lack of epidemiological surveillance and the poor diagnostic capabilities of the SEARG countries (www.searg.info/). This ties in closely with the poor data submitted in the country reports by the country representatives. However, the lack of accurate epidemiological data, as well as the poor diagnostic capabilities, has led to one of the greatest successes of the SEARG group. In 1993, SEARG began coordinating and running training exercises for various SEARG countries in diagnostic techniques, including standardisation among the various countries. The most recent of these exercises was in 2009. These diagnostic training workshops have been run in collaboration with, and sponsored by, the World Organisation for Animal Health (OIE) in order to standardise OIE veterinary diagnostic protocols among the countries. Fourteen of these countries participated in the most recent training workshop, in which each country’s standard operating procedure (SOP) was submitted to the coordinators of the workshop. The SOPs were then compared with one another and several steps in the SOP varied significantly between laboratories. After determining and testing the efficacy of each protocol, a harmonised and standardised OIE diagnostic protocol was finalised and published with the financial support of the Food and Agricultural Organization (FAO) of the United Nations. To follow through and continue this philosophy, and again supported by the OIE, proficiency testing of diagnostic facilities of 12 SADC countries commenced in July 2011. As an outcome of the resolutions of the 2011 SEARG meeting in Mozambique, a programme to evaluate the potential implementation benefits of the direct rapid immunohistochemical test as a component within the diagnostic capability of African rabies laboratories was initiated (www.searg.info/).

Another important concern in Africa is the lack of governmental support for rabies (and other neglected disease) control. This concern has been raised at several meetings (2001, 2003, 2006). The aim of the SEARG group is to be self-sustained through government support, and any funding it receives from non-governmental organisations should be aimed at funding projects in rabies control. The SEARG group, through outside funding, has been able to sponsor delegates from each Member Country to attend the bi-annual meetings. However, there has been a strong movement towards trying to gain governmental support, so that each Member Country’s government sponsors its own representative. At the most recent SEARG meeting (2011), attended by 89 delegates, several representatives were sponsored by their own governments to participate, suggesting that governments have been responding to calls for more support and/or that SEARG participants are becoming more pro-active in ensuring their own participation.

Continuing constraints documented at the Southern and Eastern African Rabies Group Meeting 2011

Although SEARG has had many successes, the group also has several shortcomings. The main problem has been the collaboration of the medical sectors with the veterinary sectors – the One Health approach. Initially, members from the medical sector attended SEARG meetings but, through the years, there has been a gradual decline in participation from the medical sector (in recent years SEARG has sponsored only one delegate per country, from veterinary health) and very few such representatives were in attendance at the most recent 2011 SEARG meeting. The issue of the One Health approach has been raised several times, and yet there has been no significant action by Member Countries or the SEARG group.

At the most recent meeting in Mozambique, 2011, FAO representatives distributed a questionnaire about SEARG and what delegates considered to be important challenges and successes (www.searg.info/). The questionnaire also encouraged suggestions on the way forward for SEARG. Most delegates felt that SEARG was an important forum for rabies experts and provided useful information as well as guidance. However, most people reiterated the point that other sectors (e.g. medical, wildlife, ecologists, sociologists, etc.) need to be part of the SEARG meetings, emphasising the requirements for a genuine One Health approach.
Showcase projects and their implications for the region: the Bill and Melinda Gates Foundation/World Health Organization rabies control programme

A significant step in raising the profile of rabies in the developing world was the launching of pilot programmes that are geared towards the elimination of rabies in dogs. These programmes were the initiative of the Global Alliance for Rabies Control (GARC) and the Partners for Rabies Prevention (PRP), who, together with the World Health Organization (WHO), obtained funding from the Bill and Melinda Gates Foundation (BMGF) for three such showcase programmes. The three sites are in the Philippines in Asia, in south-eastern Tanzania and in the Kwa-Zulu Natal province in South Africa.

This programme, partially funded by the BMGF and administered by WHO, aims to eliminate human rabies cases through the control and eventual elimination of canine rabies (1, 19). Each programme will run for a period of five years (19) and will serve as a platform for generating information on the unique challenges and solutions facing each site, with a view to extending these projects to neighbouring regions. It is estimated that eliminating rabies in these three areas will save in excess of 50 million people from the constant fear of rabies (19).

African showcases: United Republic of Tanzania project

The project area in south-eastern Tanzania houses close to 6.5 million people and approximately 430,000 dogs (12). Challenges reported include difficulties in the allocation and management of funds, the presence of rabies in wildlife hosts (19) and poor knowledge of the proper use of rabies immunoglobulin (12). However, this project has also led to innovative solutions, such as the use of mobile phone technology to collect case data from the field (11). This allows automated vaccine stock management and also aids in the monitoring of disease incidence and the efficacy of control efforts (12). A total of 36,549 dogs have already been vaccinated, and it is to be hoped that the momentum and knowledge gained will ensure sustainability of the project in the years to come. An important aspect influencing this sustainability is the involvement of the Tanzanian Government – external funding is finite, but the risk of the reintroduction of rabies, once it has been eliminated, is not. Already, the first steps toward long-term sustainability have been taken, through education initiatives and the employment of Tanzanian residents in the programme.

African showcases: Kwa-Zulu Natal project

The project in South Africa focuses on the province of Kwa-Zulu Natal (KZN). Among the reasons for the selection of this site as a BMGF/WHO project area were:

(i) classical dog rabies is endemic in this part of Africa

(ii) this region has a good record of rabies surveillance, which has been well documented since the 1970s

(iii) the disease burden in dogs and humans is well supported by laboratory diagnosis

(iv) there is a general understanding of the epidemiology of rabies in this region, including the molecular epidemiology

(v) while it is a challenging environment, these challenges are typical over much of the African continent

(vi) there have been proven, government-driven efforts to control the disease in dogs.

From the outset, the intention of these showcase projects has been the quest for research components and the implementation of new technologies to improve strategies for dog rabies control.
that would enable the eventual elimination of rabies in dogs. For KZN, these research activities include aspects of vaccinology, epidemiology, wildlife involvement, diagnostics, animal primary health, human health, dog ecology and the expansion of the programme into the wider immediate region, including neighbouring countries.

The benefits of international interest in the KZN rabies control programme were evident from early on, and it was possible to intensify vaccination campaigns in strategic areas. In the southern parts of KZN, the traditional stronghold of rabies, a 48% reduction in dog rabies was evident one year into the BMGF/WHO project. This trend continued and a steady decline in rabies cases has persisted over the three years that the project has now been running. Recent epidemiological research also demonstrated a north-east trend in the occurrence of cases. As hotspot areas in the south of KZN become rabies free, those cases in the more remote northern areas become more evident and can become targets in the next phase of the programme.

A fundamental goal of the BMGF/WHO programme is human rabies prevention. In terms of this challenge, the KZN programme has achieved significant success. Indeed, KZN was free of human rabies from June 2010 to September 2011 – which constitutes the first time in more than 20 years that KZN has been free of human rabies for a period longer than one year. While there was another confirmed human case after 15 months, and the disease is far from completely eliminated, the tangible progress and projected outcome of the programme are very encouraging and offer hope for future success in the control of rabies on the African continent.

The aim of these projects is to act as a ‘showcase’ – they are only funded for five years, after which the local governments of the respective regions will have to manage and coordinate their activities and take responsibility for rabies control. However, simply extending the existing programmes is not enough – rabies is a transboundary disease, which means maintaining isolated rabies-free regions is not sustainable. Rather, the knowledge gained through this programme – both in the individual projects and by comparing the different approaches – should serve as a model for the establishment of similar programmes throughout Africa. Once a country or region has managed to eliminate dog and human rabies, the simplest way of keeping it rabies free is to transfer its skills to neighbouring regions, helping to eliminate rabies in a consolidated fashion that would prevent reintroduction. This is, however, a rather idealistic outlook. The largest hurdle to the elimination of dog and human rabies in Africa remains the lack of political will, and not the lack of funding. A key factor yet to be addressed is the importance of wildlife rabies. The United States still has wildlife rabies, yet it has been free of canine rabies for several years (18). However, the movement of domestic dogs in Africa is much less constrained, which may facilitate contact with wildlife species still harbouring rabies. African domestic dogs in rural areas are generally more frequently exposed to wildlife than those in urban areas – an important factor hindering the elimination of dog and human rabies.

Conclusions and recommendations

- Canine rabies has become widespread in Africa during the 20th Century.
- Rabies in animals and humans is seriously under-reported in Africa.
- Sustained reliable surveillance is required to demonstrate the disease burden and thus to aid in prioritising rabies control.
- SEARG, in collaboration with the global rabies community, is striving towards a pan-African approach to rabies control.
- The coordinated guidance and support of the OIE, WHO and other global partners in the ‘One Health’ approach are required.
- Regional African programmes have already demonstrated the feasibility of dog rabies control and potential elimination.
Acknowledgements

The authors wish to thank WHO, the OIE and FAO for their invaluable contributions in the African region. They would also like to thank the rabies laboratories of the CDC (C.E. Rupprecht), Animal Health and Veterinary Laboratories Agency (AHVLA) (A.R. Fooks), Friedrich-Loeffler-Institut (FLI) (T. Muller), Canadian Food Inspection Agency (CFIA) (A.I. Wandeler) and other Partners for Rabies Prevention members for their interest and collaboration in the region.

References

The reality of rabies: setting the scene


Epidemiology of rabies in Korea

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Summary

In total, 16,129 rabies cases have been recorded in Korea since the first identification of rabies in 1907. The Korean government implemented an intensive rabies control programme in the 1960s. No rabies cases were reported during the eight-year period between 1985 and 1992. However, there have been 432 cases between 1993 and 2010, since the recurrence of the disease in Gangwon-do in 1993. To prevent wild animal-mediated rabies, oral bait vaccines were employed. After bait vaccines were laid, the number of annual rabies cases seemed to decrease between 2004 and 2010. Since 2007, no rabies cases have been identified in Gyeonggi-do. However, cases continue to occur, moving eastwards to Gangwon-do. Based on the monthly distribution of animal rabies for this 18-year period (1993–2010), the incidence was highest during the winter months (December to February), with a peak in January. All Korean rabies virus (RABV) isolates collected from animals diagnosed with rabies were subjected to phylogenetic analysis. The similarities in the nucleotide sequence of the nucleoprotein (N-) gene among all Korean isolates ranged from 98.1% to 99.8%. Phylogenetic analysis showed that the Korean isolates were most closely related to the eastern Chinese strain. An epidemiological study indicated that the Korean RABV isolates originated from rabid raccoon dogs in north-eastern Asia. Preventive measures, including mass vaccination, the slaughter of stray dogs and distribution of bait vaccines, were responsible for a substantial decrease in the number of rabies cases in Korea.

Keywords

Introduction

Rabies is an important zoonosis that occurs in more than 150 nations around the world and claims the lives of approximately 55,000 people annually (9). The number of rabies deaths is increasing in Africa, Asia and Latin America, and these regions need support from other World Organisation for Animal Health (OIE) Member Countries who have successfully eliminated the disease.

Since the first rabies outbreak in a dog in 1907, rabies cases have been reported in several animal species, from several provinces of Korea, until 2010. Rabies control programmes, such as intensive vaccination of dogs with live attenuated rabies vaccine, removal of stray dogs and rabies awareness campaigns, were implemented. This led to a steady decrease in animal rabies cases between 1960 and 1984, and no rabies cases were reported for the eight years between 1985 and 1992 (4, 12).
Rabies is transmitted by several kinds of vector, including dogs, bats, raccoon dogs, wolves and mongooses, depending on the national situation (3, 5). Dogs were known to be the main vector for the transmission of rabies virus (RABV) to humans and other animals in Korea before 1984. Unfortunately, a recurrence of rabies was identified in Gangwon-do in 1993, and thereafter a continuous increase in the number of rabies cases was observed. An epidemiological study on rabies reported that wild animals, such as raccoon dogs (*Nyctereutes procyonoides koreensis*) and badgers (*Meles meles*), played an important role in transmitting rabies to cattle and dogs in Korea (8, 11). Since 1993, according to the epidemiological study, dog-to-dog transmission (urban rabies) has not been reported in Korea, but sylvatic rabies cases have continued to be identified until 2010.

In this study, the results of the rabies elimination programme, including epidemiological characterisation, which was implemented by the Korean veterinary authority during the 18 years between 1993 and 2010, are described.

**Materials and methods**

**Collection of data**

Detailed data from all animal rabies cases that had been reported to the Animal, Plant and Fisheries Quarantine and Inspection Agency (QIA) of Korea were collected from 1993 to 2010. Data on human rabies cases during the same period were collated from the Korean Center for Disease Control and Prevention. Only laboratory-confirmed cases were included in the analysis.

**Indirect fluorescent antibody test**

To diagnose rabies, the indirect fluorescent antibody test was performed, according to the procedure described by the OIE and WHO (8, 9). In brief, thin frozen sections of Ammon's horn tissue on a slide were fixed in cold acetone (–20°C) for 20 min. After incubating with specific monoclonal antibody (JenoBiotech, Chuncheon, Korea) against rabies, the slides were stained with fluorescence isothiocyanate conjugated goat-anti mouse immunoglobulin G and immunoglobulin M. Positive and negative controls were run together with the test samples. The samples showing specific fluorescence were confirmed as positive.

**Phylogenetic analysis**

For the analysis of the nucleotide sequence coding the nucleoprotein of Korean RABV, sequence data from a total of 51 Korean RABV isolates were obtained from GenBank. Phylogenetic trees were reconstructed on aligned nucleotide sequences using CLUSTAL W. The robustness of the phylogenetic analysis was determined by bootstrap analysis with 1,000 replicates. Graphic output was produced by TreeView 1.6.1.

**Virus neutralisation test**

The virus-neutralising antibody was measured in 96-well microplates by neutralising peroxidase-linked assay (2). Serum titres were recorded as the reciprocal of the highest initial dilution of sera that neutralised rabies virus replication in 100% of the wells. The serum samples showing a virus neutralisation titre higher than 1:2 were considered positive and those higher than 1:16 were considered protective against wild virus infection.

**Results**

A total of 16,129 rabies cases have been confirmed in Korea since 1907 (Figs 1 & 2). During the period between 1993 and 2010, there were 432 animal rabies cases in five different species: 191 cases in cattle (44.2%); 166 cases in dogs (38.4%); 71 cases in raccoon dogs (16.4%); 3 cases in
cats (0.7%), and a single case in a deer (0.2%) (Fig. 3). During the same period, seven human deaths associated with rabies were reported. The highest annual incidence of rabies was recorded in 2002, with 78 cases in animals, which then decreased to a median of 24 cases per year.

**Fig. 1**
*Animal rabies cases in Korea between 1907 and 2007*

Rabies was widespread and occurred in all regions of Korea until 1984. Then, without any clear explanations, there were no rabies cases in Korea from 1985 to 1992. Rabies recurred in 1993 but the disease was confined to the northern part of South Korea, in particular the provinces of Seoul, Gyeonggi-do and Gangwon-do.

**Fig. 2**
*Number of human and animal rabies cases reported in Korea between 1970 and 2010*

Rabies was widespread and occurred in all regions of Korea until 1984. Then, without any clear explanations, there were no rabies cases in Korea from 1985 to 1992. Rabies recurred in 1993 but the disease was confined to the northern part of South Korea, in particular the provinces of Seoul, Gyeonggi-do and Gangwon-do.
Fig. 3
The percentage of rabies cases in Korea, according to species, between 1993 and 1997, 1998 and 2003, and 2004 and 2010

Two of these provinces (Gyeonggi-do and Gangwon-do) are located near the border of the demilitarised zone and the rabies outbreak continued to move eastwards to Gangwon-do. Figures 4a and 4b show the spatial locations of positive animal rabies cases in South Korea during the period between 1993 and 2003, and from 2004 until 2010, respectively. In Gyeonggi-do, sporadic outbreaks of rabies were reported in nine counties (Yangju, Paju, Younchun, Pochun, Gimpo, Goyang, Kapyung, Dongduchun and Yangpyung) from 1993 to 2007.

Fig. 4
Location of reported animal rabies cases in Korea from 1993 to 2003 (4a) and from 2004 to 2010 (4b)

After this, no further cases were reported until 2010. In Gangwon-do, the disease was also intermittently reported in nine counties (Chuncheon, Hongchon, Goseong, Yanggu, Inje, Chulwon, Sokcho, Yangyang and Hwachen) from 1993 to 2007. Thereafter, from 2008 to 2010, rabies occurred in the adjacent six counties (Goseong, Sokcho, Yanggu, Inje, Yangyang and Hongchon), which are located in the eastern part of Gangwon Province. When the monthly distribution of animal rabies was analysed, the highest incidence was recorded in January and February, and the lowest incidence from June to September (Fig. 5).
The nucleotide sequence analysis showed that all of the Korean isolates were classified into genotype I of the genus Lyssavirus, with the nucleotide similarity among the 27 Korean isolates ranging from 98.1% to 99.8% (Fig. 6). Among the non-Korean rabies virus strains, Chinese strain NeiMeng1025B exhibited the highest nucleotide sequence similarity with the 27 Korean isolates, ranging between 96.1% and 96.7% at the nucleotide level. The nucleotide similarities of the Korean isolate (KRVB0902) with the Russian strain (857r) and the Sri Lankan strain (SRL1145) were 95.7% and 86.8%, respectively. A phylogenetic analysis based on the N-gene classified the Korean isolates into three subgroups (Gangwon-do I, Gangwon-do II and Gyeonggi-do) with high similarity.
The results of RABV serosurveillance in Gangwon-do are shown in Figure 7. On average, 65.3% of dogs and 43.2% of cattle were shown to be seropositive for RABV by virus neutralisation assay. Since 2005, over 60% of the dogs tested from Gangwon-do have shown seropositivity, whereas cattle from the same area show a large fluctuation in the seroprevalence of RABV antibodies.

![Figure 7: Percentage of rabies virus seropositive samples from dogs and cattle sampled in Korea between 1999 and 2010, except during the period 2000 to 2001. Bar graphs indicate the number of seropositive samples and line graphs indicate the number of animals sampled.]

To block rabies transmission by wild animals, especially raccoon dogs, the Korean veterinary authority has distributed vaccinia-rabies glycoprotein bait vaccine manually since 2000. The bait vaccines have been distributed twice a year, in spring and autumn, and collected two months after distribution. As shown in Figure 8, over three million bait vaccine doses have been distributed to the rabies-endemic areas (Gyeonggi-do and Gangwon-do) and the average intake rate of bait vaccine by wild animals was found to be 88.4% in 2010.

![Figure 8: Numbers of bait vaccines distributed to rabies-endemic areas of Korea and the average rate of intake by wild animals.]

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*Compendium of the OIE Global Conference on Rabies Control*
Before bait vaccines were distributed to the provinces at risk of rabies, Gangwon-do and Gyeonggi-do, instruction was given to those who distributed the vaccine. The baits were distributed in spring and autumn, twice a year, and checked two months after distribution for signs of consumption. The rate of intake was calculated as the percentage of the bait vaccines consumed by wild animals.

**Discussion**

Since rabies recurred in the northern part of South Korea in 1993, many rabies cases have been reported in Gyeonggi-do and Gangwon-do (7). All mammals can be infected by a rabid animal’s bite, and rabid animals show 100% mortality with a range of clinical signs. It is therefore essential to immunise animals, such as dogs and cattle that live in a region at risk of rabies with RABV vaccine. Vaccinia-rabies glycoprotein bait vaccine has been distributed to block transmission of rabies in wild animals in Korea. This preventive measure has successfully eliminated rabies in Gyeonggi-do since 2007, but the occurrence of the disease has shifted to the north-eastern region of Gangwon-do.

Over the past 18 years, rabies cases in Korea have frequently been observed in January and February. This high incidence in winter may be related to raccoon dogs foraging for food near villages and in rural areas. Indeed, it has been reported that raccoon dogs are often seen wandering around chicken farms or military units during the winter, looking for food (1). This would suggest that domestic animals are likely to be exposed to rabid raccoon dogs, especially during winter time. In contrast, the incidence of rabies cases in the summer season is relatively low, possibly due to the raccoon dogs remaining closer to their wild habitats as a result of greater food availability.

When comparing the nucleotide similarity with non-Korean isolates, the Korean RABV isolates formed a close phylogenetic relationship with the NeiMeng1025B strain, which was isolated from a naturally infected raccoon dog in the Jilin province of China. It is thus likely that RABV in Korea was transmitted from the north-eastern region of China. In addition, Korean RABV isolates can be classified into three subgroups by geographical region, i.e. Gyeonggi-do, Gangwon-do I and Gangwon-do II, with a high similarity based on phylogenetic analysis. Korean RABV isolates obtained from regions in relatively close proximity tend to cluster together.

Animals with antibody titres less than 0.5 IU/ml or virus-neutralising titres of less than 1:16 developed severe clinical signs consistent with rabies after challenge with virulent RABV. However, rabies can be prevented if seroconversion following vaccination has occurred and if antibody titres are measurable in the blood (6). Only 60% to 70% of dogs in rabies-risk regions had positive antibody titres of 1:2 or above, suggesting that reinforced vaccination programmes in dogs and cattle should be employed, to elevate protective immunity against rabies and to successfully eliminate rabies from Korea.

**Recommendations**

To eliminate rabies transmitted by raccoon dogs completely, new rabies programmes, including trap-vaccination-release, oral rabies vaccination and population reduction programmes, are expected to be applied to regions at risk of rabies in the near future.

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References


Epidemiology of rabies in Bhutan: geographical information system-based analysis

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Summary

In this study, the spatio-temporal patterns of rabies in domestic animals in Bhutan is described. Surveillance data were analysed using a geographical information system and traditional and spatial statistics. Rabies cases in animals (mostly dogs and cattle) were mainly reported in the southern parts of Bhutan, bordering India. The trend of reported cases was relatively stable until 2005, but increased during both 2006 and 2008, due to major outbreaks in eastern and south-west Bhutan. Significant clusters (P < 0.05) of high numbers of cases were observed in south-central and south-west Bhutan. There was also a significant (P < 0.05) spatial correlation between reported cases in dogs and in cattle. The rabies prevention programme should be focused on the highly endemic areas of southern Bhutan. Mass vaccination of dogs in this region would create an immune buffer (cordon sanitaire) and prevent rabies incursions into the interior of Bhutan.

Key words

Bhutan – Case study – Domestic animals – Epidemiology – Rabies – Spatial distribution.

Introduction

Rabies is one of the oldest infectious diseases known to mankind and still remains a major public health problem, causing an estimated 70,000 human deaths every year, particularly in Asia and Africa (6). Although effective post-exposure prophylaxis is available, these measures may not be affordable in many resource-limited countries (9, 22). Control of rabies in the domestic dog – the primary source of human rabies – can interrupt the transmission cycle and prevent further transmission to humans (22). For example, mass vaccination of dogs in the Serengeti District of north-western Tanzania, with vaccination coverage of 64.5%; 61.1%; 70.6% and 73.7% following each of the four campaigns between October 1996 and February 2001, resulted in a significant decline of rabies incidence in dogs, by 70% after the first campaign and by 97% after the second campaign (4). Similarly, the incidence of human bite injuries from suspected rabid dogs declined significantly in the Serengeti District after dog vaccination and reduced demand for human post-exposure prophylaxis, but not in adjacent unvaccinated districts (4). In the canine rabies-endemic area of the Phetchabun province of Thailand, mass vaccination of dogs with an annual vaccination coverage ranging from 64% to 78%, along with post-exposure prophylaxis in humans, resulted in a decline of dog rabies incidence, and no human rabies deaths were reported during the last three years (1999 to 2001) of the campaign period between 1996 and 2001 (8). Similarly, in Latin America, mass dog vaccination campaigns and human post-exposure prophylaxis carried out between 1982 and 2003 have resulted in a significant decline in
the number of rabies cases in dogs, from 15,686 cases to 1,131 (93% drop), and human rabies cases, declining from 355 to 35 (91% drop) (3, 12). These findings in the field clearly demonstrate that the human rabies incidence can be reduced or eliminated by controlling rabies in animal reservoirs.

Bhutan is a small (38,394 km²) Himalayan landlocked country, located between India to the south and the Tibetan province of the People’s Republic of China to the north. While Bhutan shares a porous border with India in the south, the Himalayan mountain ranges in the north act as a natural barrier with China. There are increasing trade activities with the free movement of people between Bhutan and India. Canine rabies is endemic in the areas of southern Bhutan that border India (14), but sporadic occurrences have been reported in other, previously rabies-free, areas (15, 16). This indicates that there is a risk of the disease re-emerging (an increased distribution or incidence) in Bhutan, if proper surveillance and control programmes are not implemented. In addition, human rabies deaths are also reported every year from the southern endemic areas of Bhutan (10). For instance, there were 15 reported human rabies deaths between 2006 and July 2011, equivalent to a cumulative incidence of 2.1 deaths per 100,000 at-risk population (with an average annual incidence of 0.28 deaths per 100,000 people) (11). The presence of rabies in southern Bhutan results in substantial financial implications for its society in the form of farm animal deaths, the expense of post-exposure prophylaxis in humans, and the cost of prevention and control programmes in animals (15, 16). There are large numbers of stray dogs in Bhutan – particularly in urban centres (freely cohabiting with humans). This poses the risk of dog bites, and results in increasing usage of post-exposure prophylaxis because all dog bites are considered a rabies risk, due to the presence of rabies in southern Bhutan (13). Although shooting and oral poisoning of dogs has been implemented for both rabies and dog population control in the past, it is not practised any more in Bhutan. A nationwide dog population and rabies control programme (capture–neuter–vaccinate–release) is ongoing in Bhutan, with the objective of sterilising and vaccinating more than 80% of the estimated 50,000 dogs, thereby reducing the stray dog population to a manageable level (7). Domestic dogs play a principal role in the transmission of rabies, and no wildlife rabies cases have been reported so far in Bhutan.

In this study, we describe the distribution of domestic animal rabies cases in Bhutan, using a geographic information system (GIS). These systems are increasingly used in public health and epidemiologic research as tools to visualise, manage, explore and analyse spatial data, providing useful information about the distribution and risk areas of disease that can inform control programmes (5, 18, 19, 21). Similarly, the information generated from this study can help to identify the risk areas which need to be prioritised in the allocation of resources for the surveillance and control of rabies in Bhutan.

**Methods**

Rabies surveillance data for the period between January 1996 and December 2009 were retrieved from the Veterinary Information System database maintained at the National Centre for Animal Health and the Regional Veterinary Laboratories of the Department of Livestock, Bhutan, as described elsewhere (14). These data included: the number of rabies cases reported in each animal species (cattle, horses, pigs, goats, cats and dogs), date of occurrence, and location (village, sub-district and district). A case is defined as an individual of any species of domestic animal (dogs, cattle, horses, pigs, goats, cats) in which rabies has been clinically confirmed, based on epidemiologic investigations or laboratory examination of brain specimens (14). The reported rabies cases in cattle and dogs over a period of 14 years (1996 to 2009) were then aggregated at the sub-district level and used in subsequent analysis. A GIS (ArcGIS 9.3 ESRI, Redlands, CA, United States [USA]) was used to visualise the spatial distribution of rabies cases in dogs and cattle. A global spatial autocorrelation (Moran’s I test) statistic (ArcGIS™ 9.0 Spatial Statistics) was used to determine whether rabies case distributions, in dogs and cattle, exhibited spatial patterns. Local clusters of cases were investigated
by estimating Anselin’s local indicator of spatial autocorrelation statistics (1, 2). A spatial interpolation analysis was also performed, using the centroid of each sub-district as a point layer, to estimate a continuous distribution of rabies cases. An inverse distance weighing (IDW) method (Spatial Analyst Tools; ArcGIS™) was used to interpolate reported rabies cases in dogs and cattle separately. The IDW is a moving average or distance-weighted average method and assumes that each interpolation surface should be influenced the most by nearby points and the least by more distant points. The IDW assumes that each measured point has a local influence that diminishes with distance. For example, to predict a value for any unmeasured location, IDW uses the measured values surrounding the prediction location (Spatial Analyst Tools; ArcGIS™ 9.3). The resulting interpolation was then displayed as a continuous, graduated colour surface of the centroid of each reported sub-district for cattle and dogs separately.

**Results**

A total of 814 animal rabies cases were reported between 1996 and 2009, with a majority of the cases in cattle (55%, 447/814) and dogs (39%, 317/814). Only a few cases were reported in other species (horses: 17; cats: 14; pigs: 13; and goats: 6) (see Table I) (14). The number of reported cases was relatively stable until 2005, but increased in 2006 and 2008, due to major outbreaks in eastern and south-west Bhutan.

**Table I**

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Figure 1 illustrates the monthly distribution of reported rabies cases in animals. Of the total 20 districts and 205 sub-districts in Bhutan, 11 districts and 59 sub-districts reported rabies between 1996 and 2009. Cases were commonly reported in southern Bhutan. The distribution of reported rabies cases was strongly clustered in both dogs ($I = 0.153; \ P = 0.004$) and cattle ($I = 0.144; \ P = 0.004$). Local indicator of spatial autocorrelation (LISA) statistics identified significant clusters ($P < 0.05$) of high numbers of cases in both dogs and cattle in south-central and south-west Bhutan.
The reality of rabies: setting the scene

Fig. 1
Cumulative monthly distribution of reported rabies cases in domestic animals in Bhutan, 1996 to 2009

The interpolated map shows high numbers of reported cases in southern and eastern Bhutan (Figs 2 & 3). There was a significant ($P < 0.05$) spatial correlation of reported cases in both dogs and cattle, as illustrated in Figures 2 and 3.

Fig. 2
Spatial distribution of rabies cases in domestic dogs in Bhutan during the period 1996 to 2009, interpolated by inverse distance weighing

Fig. 3
Spatial distribution of rabies cases in cattle in Bhutan during the period 1996 to 2009, interpolated by inverse distance weighing
Discussion

In this study, we conducted descriptive and GIS-based exploratory spatial analyses to describe the spatial distribution of rabies in domestic animals and to identify rabies risk areas in Bhutan. There were a higher number of reported cases in cattle than in the reservoir species (domestic dogs). This can be explained by the surveillance system used, in which there is no active surveillance of rabies in domestic dogs, especially stray dogs. Rabid stray dogs are difficult to trace, due to transborder movement in the southern border towns of Bhutan. In addition, rabid stray dogs can be killed by vehicles or people, and remain unreported to the veterinary authorities. In contrast, cases in cattle and other domestic animals are effectively captured by the reporting system, because of the greater economic value of these animals (14). It is also possible that a single rabid dog might be involved in infecting many cattle that are usually let out on open-field grazing areas. This could happen, especially during major rabies outbreaks, as has been demonstrated during outbreaks in eastern Bhutan and south-west Bhutan, where large numbers of cattle have died of rabies following exposure to rabid dog bites (15, 16).

Our analysis confirmed a significant spatial distribution of rabies in Bhutan, with increased incidences in southern Bhutan. The results suggest that rabies endemicity has been maintained among stray or free-roaming dogs in the southern border areas, or that this endemicity could be the result of transborder movement or translocation of infected dogs between South Bhutan and Indian border towns. This is confirmed by phylogenetic studies which show that the rabies virus strain circulating in southern Bhutan is closely related to Indian rabies virus strains (17). According to LISA statistics, clusters of rabies cases (in both cattle and dogs) were identified in the south-central and south-western regions of Bhutan. Identification of these clustered areas will help to focus the investigation of risk factors and direct the organisation of an effective control programme. We recommend that mass vaccination of dogs with >70% coverage should be focused and prioritised in these highly endemic areas in southern Bhutan to optimise the use of limited resources. Prevention of rabies in these ‘hot spots’ and endemic areas would eventually eliminate and reduce the incidence of rabies in dogs and humans, since no wildlife reservoir of rabies has been reported in Bhutan. Mass vaccination of dogs in these areas would create an immune belt (cordon sanitaire) and prevent rabies incursions into the interior of Bhutan. For example, Malaysia successfully eradicated canine rabies by mass vaccination and a stray dog reduction programme in the 1950s and its rabies-free status has been maintained by vaccinating dogs within an immune belt along the Thailand-Malaysia border, despite rabies remaining endemic in Thailand (20). This should serve as a model for Bhutan to plan for a rabies elimination programme at the India–Bhutan border. Furthermore, a disease surveillance and monitoring programme should be prioritised in rabies-endemic southern Bhutan.

In conclusion, the GIS-based spatial analysis clearly indicates that the risk of rabies incidence in dogs and other domestic animals exhibits a regional trend, particularly in southeast, south-central and south-west Bhutan. The identification of rabies risk areas and their spatial visualisation as a risk map in this paper is useful for prioritisation of rabies surveillance and control activities in Bhutan. Therefore, disease risk mapping is a valuable tool for understanding the spatial distribution of rabies cases and to identify highly endemic areas for future public health planning and prioritising resource allocation for control programmes.
Recommendations

- Mass vaccination of dogs with > 70% coverage should be focused and prioritised in the highly endemic areas in southern Bhutan to create an immune belt (cordon sanitaire) and prevent rabies incursions into the interior of Bhutan.
- A regionally coordinated rabies control programme is necessary in the border areas between Bhutan and India to eliminate rabies in Bhutan.
- Inter-sectoral coordination and cooperation is necessary for the prevention and control of rabies in Bhutan.
- Epidemiological surveillance of rabies should be improved by laboratory confirmation of cases, and the data thus generated should be shared between the public health and veterinary sectors and also internationally through the World Organisation for Animal Health (OIE).
- Rabies surveillance should be extended to wildlife to confirm the presence or absence of rabies or rabies-related viruses in wildlife in Bhutan.

References


Molecular tools for rabies diagnosis in animals

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Summary

Advances in the study of molecular biology have provided cost-effective technological initiatives that have supported the development of sensitive and specific techniques for rabies diagnosis. In particular, using tests based on the polymerase chain reaction (PCR), it is possible to analyse large numbers of samples in a single day. Developments in reagents and procedures have allowed improvement in the standardisation of techniques, leading to high test sensitivity and specificity. For these reasons, a validated PCR-based test should be considered by the World Organisation for
Animal Health (OIE) as an alternative test for rabies, and included in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals.

Keywords


Introduction

Rabies is caused by all members of the genus *Lyssavirus* (Family *Rhabdoviridae*). Rabies virus (RABV) is the predominant global species, with various host reservoirs, dogs being the most important.

Preliminary clinical diagnosis of rabies in animals is undertaken by veterinarians, based on the signs, available history and epidemiological information associated with each suspect case. However, a clinical diagnosis for rabies in animals is not reliable as there are no clinical signs that are pathognomonic for rabies. In addition, there are no characteristic gross pathological lesions associated with rabies. In most animals, microscopic non-specific lesions with ganglioneuritis may be observed in the nerve centres, as well as histiolymphtocytic cuffs and gliosis, but these are suggestive of viral encephalomyelitis and are not exclusive to rabies. The most prominent lesions are usually observed in the cervical spinal cord, pons and hypothalamus. The only specific microscopic changes are intracytoplasmic eosinophilic inclusions (Negri bodies) corresponding to the aggregation of developing rabies virus particles, but their absence does not preclude *Lyssavirus* infection. These pleomorphic neuronal inclusions, measuring from 4 μm to 5 μm, are usually located in the hippocampus. Consequently, diagnosis can only be confirmed by laboratory tests, conducted post mortem on central nervous system tissue removed from the cranium. Diagnosis by demonstration of Negri bodies is no longer recommended as a primary test, due to the insensitivity of this method.

The current gold standard World Organisation for Animal Health (OIE) prescribed test is the direct fluorescent antibody test (FAT). For this test, the medulla oblongata, cerebellum and hippocampus are the recommended tissues of choice (9).

Currently recommended confirmatory tests are based on virus isolation, using either the rabies tissue culture infection test (RT CIT) or the mouse inoculation test (MIT). While the FAT can be completed in less than two hours, both the RTCIT and MIT require longer turnaround times (4 days and 28 days, respectively) (Table I). The MIT involves the intracerebral inoculation of mice with a clarified supernatant of a homogenate of brain tissue (medulla oblongata, cerebellum, hippocampus, cortex). Clinical signs of rabies (indicating a positive result) can be observed as early as six to eight days for RABV, and a positive FAT on the brains of the mice confirms the diagnosis. Mice should be observed for a period of at least 28 days for the development of clinical signs. This in vivo test is time-consuming, expensive and involves the use of many animals. In vitro virus-isolation tests, such as the RTCIT, involve the inoculation of the sample into a susceptible cell line, such as a neuroblastoma cell line. The same fluorescein isothiocyanate conjugate used in the FAT can then be used to confirm the presence of *Lyssavirus* antigens in the infected cell monolayers. The use of virus isolation (RTCIT/MIT) may be recommended from a sample where there is suspicion of infection with RABV, especially to confirm inconclusive FAT results and in cases of human exposure. One advantage of virus-isolation assays is the amplification of the virus isolate for subsequent typing and analysis, enabling the potential detection of viruses other than lyssaviruses. Both the RTCIT and MIT are prescribed by the OIE. However, the former is preferable because of the shorter turnaround time to achieve a result and because the test does not involve the use of animals.
Table I

Tests prescribed by the World Organisation for Animal Health

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<th>Category/description</th>
<th>Minimum performance time</th>
<th>Turnaround time [a]</th>
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<tr>
<td>FAT (antigen detection)</td>
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<td>1 day</td>
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<tr>
<td>RTCIT (virus isolation)</td>
<td>Confirmatory</td>
<td>4 days (interim positive results possible at 24, 48, 72 h)</td>
<td>4 days</td>
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<tr>
<td>MIT (virus isolation)</td>
<td>Confirmatory</td>
<td>Up to 28 days</td>
<td>Up to 28 days</td>
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<tr>
<td>RT-PCR (RNA detection)</td>
<td>Confirmatory</td>
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<td></td>
<td>30 h hemi-nested PCR</td>
<td></td>
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<tr>
<td>Real-time RT-qPCR (RNA detection)</td>
<td>Confirmatory</td>
<td>8 h for detection</td>
<td>1 day</td>
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[a] Turnaround times are the times by which a result would normally be available

FAT: Fluorescent antibody test
MIT: Mouse inoculation test
PCR: polymerase chain reaction
RTCIT: rabies tissue culture infection test
RT-qPCR: reverse-transcription quantitative polymerase chain reaction

The application of molecular biology has aided in the development of tests that result in a more rapid and sensitive diagnosis of infection with lyssaviruses (in particular, RABV). These molecular tests could be used for ante mortem diagnosis of humans and degraded or putrefied tissue, and enable genetic characterisation. As a result, rapid, differential, flexible molecular assays are becoming more widely accepted (3). For generic approaches intended to detect all lyssaviruses, cocktails of primers facilitate either hemi-nested or fully nested amplifications. Alternatively, strain-specific reverse-transcription polymerase chain reactions (RT-PCRs) have been developed to distinguish between various RABV variants in a particular geographical region. By employing fluorogenic probes, the detection of sequence-specific templates can be achieved in real time. In such assays, specificity is ensured by an inherent hybridisation reaction, and cross-contamination is avoided, due to the closed-tube nature of the test. Subsequently, for RABV and other lyssaviruses, various real-time quantitative PCR assays using TaqMan® technology have been reported.

The challenges for rabies diagnostic test developers, beyond a specific and sensitive test, are twofold: firstly, to achieve internationally accepted validation of a test that will lead to its acceptance by organisations globally; and secondly, by ensuring that tests are affordable and require minimal expertise and facilities as these tests are primarily needed mainly in developing regions where financial and logistical barriers may hinder their implementation (3). These barriers are not insurmountable and it is our expectation that, if such tests are accepted and implemented where they are most needed, they will provide substantial improvements for rabies diagnosis and surveillance of this neglected disease.

Materials and methods

Ribonucleic acid extraction

The target of rabies molecular testing is the detection of the viral RNA genome. Viral RNA is extracted from a specimen prior to molecular testing. The viral RNA is non-infectious and can be removed from high-containment laboratories for analysis. The choice of extraction technique is dependent upon the specimen (liquid or tissue) and volume of testing (manual extraction versus automated robotics). Tissue lysis and nucleic acid extraction may be chemical, using a TRIzol™ reagent (containing phenol and guanidine isothiocyanate) and chloroform, or enzymatic, with the addition of magnetic beads, filter
tubes, etc., for elution of nucleic acids. Some tissue may require pre-treatment with proteinase K and detergents such as sodium dodecyl sulphate to remove excess protein, whilst some specimens (with low cellular content) may benefit from the addition of carrier RNA prior to extraction (18).

Real-time quantitative reverse-transcription polymerase chain reaction (RT-qPCR)

For RABV and other lyssaviruses, various RT-PCR assays using a quantitative real-time platform have been described (Table II). These sensitive and specific assays are undertaken in a single step in a closed-tube system, thereby substantially decreasing the risk of contamination and potentially allowing for the characterisation of unknown isolates. Such real-time assays can be applied quantitatively and the use of an internal control (e.g. beta-actin RNA or 18S ribosomal RNA) enables the quality of the total RNA template to be assessed, thereby minimising false negatives associated with poor sample quality. All real-time RT-qPCR assays are based on a primer pair, which amplifies a small (usually <200 base pair) amplicon, which is detected in ‘real time’ either by a specific probe (TaqMan©) or a DNA-binding cyanine dye, such as SYBR Green, as the assay is in progress. It is preferable that the primer pair is designed to be pan-Lyssavirus in specificity, i.e. validated against a large panel of representative lyssaviruses covering all known Lyssavirus species, with probes specifically designed to discriminate between classical RABV and the other members of the Lyssavirus genus (18). However, the genetic diversity among lyssaviruses, even within conserved genomic regions, has precluded the use of a single probe-based assay to reliably detect all lyssaviruses.

Table II

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<td></td>
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<tr>
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<td>F</td>
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<td>943-963</td>
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<td>R</td>
<td></td>
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<td></td>
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<td>NCSK</td>
<td>F</td>
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<td>GGTGAAACCACGAGGTCGACAG</td>
<td>1189-1209</td>
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<td></td>
<td>R</td>
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<td>R</td>
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<tr>
<td></td>
<td></td>
<td>P</td>
<td></td>
<td>CGGAGGCAGTCTATAC</td>
<td>1202-1219</td>
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</tbody>
</table>

The genome of lyssaviruses is approximately 11,000 base pairs in length. For RABV, the nucleoprotein gene is located at position 71–1423 (GenBank accession number M13215).

ABLV: Australian bat Lyssavirus
DUVV: Duvenhage virus
LBV: Lagos bat virus

The validation of probe-based assays relies heavily on the availability of representative viruses or nucleic acid. However, for some Lyssavirus species, only a single virus isolate or sequence is

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**The genome of lyssaviruses is approximately 11,000 base pairs in length. For RABV, the nucleoprotein gene is located at position 71–1423 (GenBank accession number M13215).**

**MOKV:** Mokola virus
**PCR:** polymerase chain reaction
**RABV:** rabies virus
**F:** Forward primer
**R:** Reverse primer
**P:** Probe

**The validation of probe-based assays relies heavily on the availability of representative viruses or nucleic acid. However, for some Lyssavirus species, only a single virus isolate or sequence is...**

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**Compendium of the OIE Global Conference on Rabies Control**
available for primer/probe design, and may not be representative of all currently circulating or emerging variants. In addition, a single mutation in the region of the primers or the probe may alter the sensitivity of the assay, thus demanding continued vigilance and validation. This is particularly relevant when testing in animals because all of the most recently detected lyssaviruses since the report of Australian bat Lyssavirus in 1998 have been in animals not humans. Therefore, to reduce the possibility of failing to detect a novel or variant Lyssavirus, the use of universal pan-Lyssavirus primers in conjunction with SYBR Green, rather than specific probes, is perhaps the optimum confirmatory assay for the rapid real-time detection of all the known Lyssavirus species (5). As the application of real-time assays has become more widespread and routine, the availability of commercial master mixes is increasing, whereby operators simply add their local primers, probes and RNA. The use of such one-tube reagents reduces set-up times, increases reproducibility and may assist efforts to standardise and harmonise these assays. There is still no consensus on the particular region of the Lyssavirus genome to target for PCR-based assays. The majority of laboratories however, have chosen to target the nucleoprotein gene (N-gene). This is due to the large number of N-gene sequences available publicly, the relative sequence conservation across the N-gene and the abundance of N-gene messenger RNA (Table II).

Results

The real-time assay amplification curve illustrates a ten-fold dilution series of RNA extracted from RABV (CVS-11), using pan-Lyssavirus primers JW12 and N165-146 in a real-time SYBR Green RT-qPCR assay (Fig. 1) (Table II). Figure 1 demonstrates that total RNA with a concentration of 1 µg/µl is detected before cycle 20 (Ct < 20), and this assay is able to detect viral RNA at least up to a dilution of 0.01 ng/µl (0.00001 µg/µl) before cycle 40.

Fig. 1
RT-PCR amplification curve for serially diluted RABV (CVS-11 strain) RNA*

* The 1:10 serial dilution starting at 1 µg/µl and finishing at 10 pg/µl.
Two negative controls were included, showing no detectable fluorescence

# The Ct (cycle threshold) is defined as the number of cycles required for the fluorescent signal to cross the threshold (i.e. exceeds background level). Ct levels are inversely proportional to the amount of target nucleic acid in the sample (i.e. the lower the Ct level the greater the amount of target nucleic acid in the sample).
The high sensitivity of this assay has enabled it to be successfully employed in the United Kingdom (UK) for the rapid diagnosis and *Lyssavirus* species confirmation of multiple European bat lyssavirus (EBLV)-2 infected bats, the *intra vitam* detection and genetic typing of a human rabies case within five hours of sample receipt, and the detection of a rabid puppy in UK quarantine during 2008 (data not shown).

**Discussion**

Irrespective of the outcome of any clinical diagnosis, the conventional OIE diagnostic tests are entirely dependent on the nature and quality of the sample supplied. Validated OIE diagnostic tests that confirm the presence of RABV or other lyssaviruses have been the foundation of rabies control strategies in many countries (19). Prescribed tests are required by the *OIE Terrestrial Animal Health Code (Terrestrial Code)* for the international movement of animals and animal products, and are considered optimal for determining the disease status of animals. Alternative tests are those that are suitable for the diagnosis of disease within a local setting and can also be used in the import/export of animals after a bilateral agreement.

Diagnosis of rabies is undertaken using OIE-prescribed tests, usually by FAT in the first instance, with a confirmatory diagnosis based routinely on virus isolation, if necessary. The FAT test detects *Lyssavirus* antigens (nucleoprotein) with fluorescently labelled antibodies in samples of brain tissue taken from a suspect animal. The FAT is regarded as the gold standard OIE test for rabies diagnosis and gives reliable results on fresh specimens within a few hours in 95% to 99% of cases. It is the only OIE-approved direct validated method that allows the identification of *Lyssavirus*-specific antigens in a short time and at a reduced cost, irrespective of geographical origin and status of the host. It should be regarded as the first step in diagnostic procedures for all rabies laboratories. Autolysed samples can, however, reduce the sensitivity and specificity of the FAT and other diagnostic tests. When the FAT is inconclusive, it is imperative that rabies diagnosis is obtained using separate OIE-prescribed diagnostic assays (Table I). A second test is required because, on rare occasions, a single test that appears to be negative, even when the sample is taken late in the disease, has at times proven to be unreliable, resulting in a false-negative test result. These OIE-prescribed methods have provided accurate and timely information on animal rabies cases, thereby supporting surveillance for rabies and providing a greater understanding of the epidemiology of this disease. For numerous laboratories in rabies-endemic regions in the developing world, cost and simplicity are vital factors in the delivery of disease diagnosis and cannot be neglected, even when the principal consideration is for rapid diagnosis. Therefore, cost and simplicity need to be considered if new technologies are to be adopted in the regions of the world where they are most needed (3).

Owing to the neurotropic nature of RABV and other lyssaviruses, infection results in enormous viral replication in the central nervous system in the final stage of the disease, which leads to significant antigen and viral genome concentrations. This makes the detection of viral RNA in brain tissue by molecular tests an unambiguous indicator of infection. As for the detection of viral genome, molecular approaches are now available which process multiple specimens from nucleic acid extraction through to genetic typing, with considerably reduced risks of contamination. It is evident that RT-PCR dominates genetic detection of *lyssaviruses* and it seems probable that this technique will continue to dominate rabies diagnosis in the 21st Century (3). ‘Real-time’ quantitative RT-qPCR techniques allow the visualisation of results as they occur during the amplification and, with some development, enable quantification of genomic RNA in the original sample. However, the highly sensitive nature of RT-qPCR assays to detect very low levels of target molecules also renders such tests extremely sensitive to contamination by extraneous nucleic acids. It is therefore essential that all laboratories employing PCR-based assays have stringent laboratory quality control standards that reduce, as far as is practicably possible, the risk of sample or test contamination. These do not have to involve
expensive infrastructure, but include a ‘clean’ area containing all equipment necessary for reagent and test preparation and a separate area with dedicated equipment for amplification and analysis. Gloves must be worn and replaced frequently at all stages of the procedure, thereby protecting the specimens and reagents from contamination by ubiquitous RNAses and cross-contamination by nucleic acid. Good laboratory practice must be adhered to throughout the entire process, with appropriate use of positive and negative controls for each stage of the process. Reverse-transcription PCR generates DNA amplicons, with sequences that can be defined. While this adds further cost and another level of technology, it has proven invaluable in assessing the specificity of the test and has contributed to numerous epidemiological studies on RABV. The importance of sequencing PCR products was highlighted for a highly sensitive nested RT-PCR that yielded host genomic amplicons of the same size as the target amplicons, but this result was only confirmed as a false positive following direct sequencing (7). False negatives and inefficiencies in sample extraction can be determined using a housekeeping RT-PCR, e.g. β-actin or 18s ribosomal RNA (rRNA) (3).

A further benefit of RT-PCR has been for the detection and classification of novel members of the Lyssavirus genus. The genetic characterisation of new viruses has been realised with the use of molecular tools such as PCR. This has been highlighted through the detection of rabies in an African civet (Civettictis civetta) from Tanzania (11). Following the clinical suspicion of rabies in the African civet, infection was confirmed using a Lyssavirus antigen detection method. Molecular analysis of brain samples subsequently demonstrated the infection to be caused by a novel and highly divergent Lyssavirus (11).

Human rabies diagnosis based on clinical symptoms is also unreliable, and contributes to the gross under-reporting of rabies (10). From a human health perspective, assays have been developed that measure RNA in ante mortem nuchal skin biopsies and in brain biopsies taken at autopsy using real-time quantitative PCR-based techniques, although these tests are not recommended by the World Health Organization (WHO) for routine ante / post mortem diagnosis of rabies (17). In addition, as for diagnosis in animals, strict quality control standards, including the development of international standards, are required in laboratories employing PCR-based technologies that undertake human rabies diagnosis, to avoid false-positive results.

There are numerous examples of technology transfer between diagnostic rabies laboratories in developed and developing countries that have successfully demonstrated the feasibility of undertaking rabies diagnosis using PCR-based technologies. With strict quality control procedures in place, and demonstrable experience and expertise, these molecular techniques have been successfully applied for confirmatory rabies diagnosis in animals in Africa (Tanzania, Namibia, Ghana, Nigeria) China and Turkey. The OIE Twinning Programme has prompted the OIE reference laboratory in Germany to assist in preparing a laboratory in Turkey as a potential future OIE reference laboratory supporting rabies diagnosis in the Middle East region. Moreover, the OIE Twinning Programme, in collaboration with the OIE Reference Laboratory in the UK, has assisted China to meet the requirements as an OIE reference laboratory for rabies (2). In 2012, the OIE officially approved the Changchun Veterinary Research Institute in China as a recognised OIE Reference Laboratory supporting rabies diagnosis in Asia.

With the introduction of laboratory accreditation, quality control measures are being implemented in an increasing number of diagnostic facilities worldwide. Such quality controls for diagnostic rabies RT-qPCRs should encompass several measures, such as the inclusion of appropriate positive, negative and inhibition controls in assay runs, monitoring of equipment performance and staff training. For an assay to be accepted as a confirmatory test, both sensitivity and specificity analyses are crucial to avoid false-negative and false-positive test results. The consistency and the inter-assay reproducibility should also be ensured over time by monitoring test performance using blinded proficiency testing. When used with appropriate quality controls, RT-qPCR has shown comparable or
superior concordance of results compared to the prescribed laboratory tests in inter-laboratory trials. In the 2009 European Union (EU) ring trial, RT-qPCR showed 91% concordance between laboratories, compared to 87% for FAT and 70% for RTCIT (15). For these reasons, it is likely that international bodies will accept the use of molecular tests for routine rabies diagnosis in the future. However, the lack of standardisation is a major obstacle to the general use of PCR for rabies diagnosis, especially in developing countries. It is important to highlight the fact that the quality control measures discussed above are equally important, and should already be implemented in any current OIE Reference Laboratory performing FAT. The use of PCR should not be restricted only to a confirmatory diagnostic test for decomposed samples but should also be recognised as a powerful tool for virus typing and molecular epidemiology studies (8). There are a number of diseases for which PCR-based assays have been accepted by the OIE for international trade as either prescribed tests (e.g. bluetongue virus [BTV] and Infectious bovine rhinotracheitis) or alternative tests (e.g. enzootic bovine leukosis virus, malignant catarrhal fever and African horse sickness), for the diagnosis of specific animal diseases (Table III).

For other viral diseases, the presence of virus-specific nucleic acid does not always indicate the presence of infectious virus. For example, non-infectious virus (or defective virions) could also be detected by PCR (e.g. the detection of BTV RNA in the blood long after the virus can be isolated) (5). There is, however, no evidence for this situation in lyssavirus-infected animals, due to the fact that lyssaviruses do not cause viraemia in infected animals, simplifying the interpretation of PCR-based results.

Further simplification and standardisation of molecular diagnostic techniques will allow their increased application in developing countries. It is likely that new developments will focus on generating low volume and yet affordable diagnostic tests for rabies. In the future, these technologies will have a demonstrable impact on people living in developing countries, especially where rabies is still considered a ‘neglected’ disease.

Table III
Diseases listed by the World Organisation for Animal Health for which polymerase chain reaction-based assays have been accepted as either a prescribed or alternative assay for international trade (20)

<table>
<thead>
<tr>
<th>Terrestrial Code Chapter No.</th>
<th>Disease name</th>
<th>Prescribed tests</th>
<th>Alternative tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.3</td>
<td>Bluetongue</td>
<td>RT-qPCR</td>
<td>Not available</td>
</tr>
<tr>
<td>2.4.11</td>
<td>Enzootic bovine leukosis</td>
<td>Not available</td>
<td>PCR (pro-viral DNA)</td>
</tr>
<tr>
<td>2.4.13</td>
<td>Infectious bovine rhinotracheitis / infectious pustular vulvovaginitis</td>
<td>PCR (BoHV-1 DNA)</td>
<td>Not available</td>
</tr>
<tr>
<td>2.4.15</td>
<td>Malignant catarrhal fever</td>
<td>Not available</td>
<td>PCR (AIHV-1 &amp; OvHV-2 DNA)</td>
</tr>
<tr>
<td>2.5.1</td>
<td>African horse sickness</td>
<td>Not available</td>
<td>Real time RT-qPCR (AHSV RNA)</td>
</tr>
</tbody>
</table>

AHSV: African horse sickness virus
AIHV: Acelaphine herpesvirus
BoHV: Bovine herpesvirus
OvHV: Ovine herpesvirus

PCR: Polymerase chain reaction
RT-qPCR: Reverse-transcription quantitative polymerase chain reaction
**Recommendations**

- Rabies should be considered a notifiable disease in all countries.

- The OIE should consider the recommendation of a validated PCR-based test that enables rapid *Lyssavirus* detection and typing with the option of quantification in real time as an alternative test for rabies. This should be included in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals.

- Collaborative projects and technology transfer of rabies molecular testing that link laboratories from developed and developing countries should be encouraged.

- Training in both OIE alternative and newly developed diagnostic tests for rabies should be supported financially, with logistical support, by national governments in partnership with the OIE and the OIE Reference Laboratory network.

- Standardised diagnostic procedures as prescribed by the OIE should always be used to confirm a ‘suspected’ clinical case of rabies in animal(s).

- All rabies diagnostic laboratories should follow the OIE guidelines for quality assurance in veterinary laboratories.

- All laboratories equipped to undertake rabies diagnosis should participate in inter-laboratory ring trials and proficiency schemes.

**Acknowledgements**

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**References**


Criteria for parenteral and oral immunisation of dogs against rabies

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Summary

Decades of large-scale application of veterinary rabies vaccines have generated convincing evidence that vaccinating major rabies vectors is one of the most effective means to control terrestrial animal rabies. For the control of dog-transmitted human rabies, accurately understanding rabies epidemiology, clearly defining ways by which to gain access to and optimising vaccine coverage in the targeted dog population, all while assuring and preserving vaccine quality for an optimal immune response of individual dogs throughout the vaccination campaigns, are crucial success factors, as are good rabies awareness in the human population and a strong, long-term political focus on this deadly disease.

Keywords


Introduction

Preventive vaccination against the rabies virus is a highly effective method for avoiding rabies in animals and humans. Systematic and large-scale use of injectable vaccines in dogs, in combination with dog movement restrictions, contributed to the progressive disappearance of canine rabies from Western Europe and the United States (USA) by the middle of the last century (1). More recently, large expanses of these areas have been freed of wildlife rabies by oral vaccination.

Although parenteral canine mass vaccination programmes in regions still affected by canine rabies have significantly reduced the number of animal and human rabies cases in some countries in Latin America, Asia and Africa, other programmes are less advanced. Hence, in many countries, canine rabies prevails and authorities struggle with the logistics, funding and implementation of mass dog vaccination. Thus, tragically, canine rabies continues to claim nearly 55,000 human lives each year (17).

By improving the understanding of rabies at all levels, and ensuring the efficient use of good-quality rabies vaccines, this problem can be solved and horrendous suffering can be prevented.

Parenteral vaccines for the immunisation of dogs against rabies

Several types of parenteral rabies vaccines have been developed for veterinary use and mass canine vaccination campaigns remain the key component of any canine rabies control programme (17).

First-generation rabies vaccines are infected nerve-tissue brain homogenates, containing rabies virus inactivated by drying, phenol or formalin treatment. Nerve-tissue vaccines are characterised by a low
potency and considerable safety concerns (central nervous system [CNS] reactions). Modified live virus vaccines are based on attenuated rabies virus strains, grown on chick embryos (Flury, Kelev) or hamster kidney and porcine kidney cell culture (Street Alabama Dufferin [SAD], Evelyn-Rokitnicki-Abelseth [ERA]), and pose the risk of subsequent rabies infection. Although oral live recombinant rabies glycoprotein vaccines using vaccinia, or adenovirus vectors expressing ERA glycoprotein, have been developed, the use of parental inactivated (killed) cell culture vaccine is recommended by both the World Organisation for Animal Health (OIE) and World Health Organization (WHO) (17, 19) for mass dog rabies vaccination in countries with endemic dog rabies.

Inactivated rabies virus vaccines are produced on baby hamster kidney (BHK) or Vero tissue culture, using fixed rabies virus strains (challenge virus standard [CVS], Pasteur virus, Pitmann Moore, Vnukovo, etc.) and inactivated using \( \beta \)-propiolactone. The use of phenol and formaldehyde for inactivation is no longer authorised. The great majority of commercially available inactivated animal rabies virus vaccines are adjuvanted with aluminum hydroxide, aluminum phosphate, saponine, mineral oils or other immune-modulating substances.

In order to produce vaccines that are safe, pure and of sufficient potency, the vaccine production and control process needs to be highly standardised.

**Regulatory requirements for potency in carnivores of parenteral vaccines**

Differences exist in the regulations ruling rabies vaccine production and control in Europe, the USA and other parts of the world.

For example, regulatory requirements for immunogenicity testing and batch control of inactivated rabies virus vaccines in the USA are as follows (16).

Immunogenicity of vaccine prepared with virus at the highest passage from the Master Seed shall be established by challenge in each species for which the vaccine is recommended.

Twenty-two of 25 (88%) or 26 of 30 (86.6%) of uniform and seronegative animals vaccinated with vaccine formulated at the minimum protective dose should survive a challenge, applied one year after vaccination, to which 8 of 10 unvaccinated controls succumb.

Species other than carnivores can be tested by serology. Each batch destined for commercial use needs to be tested for inactivation (absence of residual virus), purity, safety (three animals) and potency National Institutes of Health (NIH).

In comparison, the European Pharmacopoeia (5) requires of inactivated animal rabies vaccines that 23 of 25 (92%) animals of minimum age vaccinated with a vaccine of minimum protective dose should survive the challenge to which 8 of 10 unvaccinated controls succumb (antigen confirmed in the brain). The potency for species other than carnivores can be tested by serology. The test is considered valid if the mean titre of 20 animals is 0.5 IU/ml for the observation period and fewer than 10% of animals have antibody titres of less than 0.1 IU/ml. Batch release tests include: identification (specificity), sterility, absence of residual virus, safety in animals, potency (Pharmacopoeia test in mice by challenge and serology).

Vaccines are biological products and, by nature, prone to variability. Regulatory requirements and standardisation attempt to limit this inherent variability but even vaccines produced under the same regimen may produce significantly different results (2, 3, 11, 20). Vaccines produced without strict governance are often of lower quality and may lack batch-to batch consistency.
**Vaccine choice, handling and proper use**

Effective parenteral rabies vaccines are widely available but may differ notably, depending on their origin and the regulatory framework governing their production and control (5). Using potent rabies vaccines is crucial for setting up effective disease transmission barriers in animal populations and so rabies programme managers or sourcing agents need to carefully verify the origin of rabies vaccines to avoid purchasing sub-standard or even counterfeit vaccines, which have become a major issue in recent years (7).

Once an adequately potent rabies vaccine has been obtained, care must be taken to follow the manufacturer's recommendations for proper storage and handling of the product to avoid loss of potency. Deviations from recommended storage and handling conditions, such as exposure to elevated or fluctuating temperatures, direct sunlight, microbial contamination, drying or vibrations, may have an adverse effect on the vaccine's ability to reliably induce a strong and lasting immune response. High-potency rabies vaccines appear to resist and perform better under ‘out-of-specs’ conditions often encountered in the field, although no direct comparisons have been made. Cell-culture-derived, inactivated and adjuvanted rabies vaccines should be preferred, while the use of nerve-tissue vaccines should be discontinued wherever possible because of low potency and considerable safety concerns (CNS reactions) (17, 18).

Following the success in controlling wildlife rabies in Europe and the USA, oral rabies vaccines (ORV) have been proposed for years as a potential method to vaccinate feral, roaming or otherwise difficult-to-handle dogs against rabies. So far, however, ORV have not passed the experimental stage and only one ORV has been registered for dogs so far. More research is required before such vaccines can be recommended for routine use in dogs (4).

**Variability of responses in dogs and vaccine coverage**

A single injection of an inactivated rabies vaccine generally induces virus-neutralising antibodies (VNA) within 7 to 14 days. Depending on age, size, breed and sex, individual animals may react differently (9). After reaching peak levels within 14 to 60 days, VNAs decline gradually and can decrease below the threshold considered protective (>0.5 IU) by day 60 (7). The ability of rabies vaccines produced in Europe to induce at least 0.5 IU/ml of VNA has been shown in several studies (Table I).

After a booster injection, neutralising antibody titres increase again. In general, cats develop higher titres and, among dogs, mongrels in developing countries, very young, older and larger dogs may respond more slowly and less strongly. Observations from community-based vaccination campaigns are summarised in Table II. Duration of immunity reported in the literature varies from one to two months to several years (11). This variability needs to be taken into account when measuring herd immunity and vaccination campaign success by serological follow-up. Since most dogs are accessible and susceptible to respond to parenteral rabies vaccination (8, 12), all animals, regardless of age, size, breed or sex, should be vaccinated annually (with three years' duration of immunity vaccines [3Y DOI]) to preserve appropriate herd immunity (13).
### Table I

<table>
<thead>
<tr>
<th>Reference</th>
<th>Test method</th>
<th>Sample and sampling period</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>RFFIT and FAVN</td>
<td>25,000 sera (17,693 dogs) 1993 to 2002</td>
<td>– 92.8% of dog and 98.1% of cat sera had titres above 0.5 IU</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>– peak titres were observed at 4 to 5 weeks</td>
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<td>– dogs vaccinated twice reached higher titres</td>
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<td>– titres dropped rapidly after 5 months</td>
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<td>– very young and older dogs responded less strongly</td>
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<td></td>
<td></td>
<td>– there were significant differences between vaccines</td>
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<td></td>
<td>– monovalent vaccine induced higher titres than multivalent vaccines</td>
</tr>
<tr>
<td>11</td>
<td>FAVN</td>
<td>&gt;17,000 16,073 dog sera tested</td>
<td>– 88% to 96% of dogs reached titres above 0.5 IU/ml</td>
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<tr>
<td></td>
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<td>– titres peaked at 4 weeks, rapidly drop thereafter</td>
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<td>– age and origin (haplotypes) of dog mattered</td>
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<td></td>
<td></td>
<td>– multiple vaccinations induced higher response</td>
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<td></td>
<td></td>
<td></td>
<td>– there were marked differences between vaccines</td>
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<tr>
<td>20</td>
<td>RFFIT</td>
<td>13,469 sera (10,999 dogs) 1997 to 2009</td>
<td>– There were marked differences between vaccines to reach 0.5 IU (78% to 98.5%)</td>
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<td></td>
<td></td>
<td></td>
<td>– worked better in dogs 6 months and older</td>
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<td></td>
<td></td>
<td></td>
<td>– multiple injection needed to sustain titres beyond 1 year</td>
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<td></td>
<td></td>
<td></td>
<td>– test failure rate greater in sera collected &gt; 4 months post vaccination</td>
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<td></td>
<td></td>
<td></td>
<td>– results different depending on dog age and size/breed</td>
</tr>
<tr>
<td>2</td>
<td>FAVN</td>
<td>6,789 sera 2005</td>
<td>– 91.9% of dogs had titres above 0.5 IU/ml to 120 days post vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– results significantly different depending on dog age and size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– significant differences depending on vaccine brand, number of vaccine injections and interval between vaccination and testing</td>
</tr>
</tbody>
</table>

FAVN: fluorescent antibody virus neutralisation
RFFIT: rapid fluorescence focus inhibition test

### Table II

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine</th>
<th>No. of dogs (test method)</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>TCO</td>
<td>54 Thai owned dogs RFFIT</td>
<td>– VNA positive: 96% (D14), 88% (D60), 74% (D180)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– single dose s.c. unable to maintain VNA for 1 year -Antibodies reappear 14 days after booster</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– except for D30, no significant difference in dogs vaccinated one or multiple times</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– no impact of parasites, anaemia, age, breed</td>
</tr>
<tr>
<td>14</td>
<td>TCO</td>
<td>301 Tunisian mongrels RFFIT</td>
<td>– VNA &gt; 0.5 IU/ml: 32% (D0), 73% (D30), 38% (M7), 36% (M12), 95% (M13) after booster</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– puppies do sero-convert and should be vaccinated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– 11.5% of total population impossible to vaccinate</td>
</tr>
</tbody>
</table>
Scientific advances: current and future tools available for rabies control

**Table II (cont.)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vaccine</th>
<th>No. of dogs (test method)</th>
<th>Key findings</th>
</tr>
</thead>
</table>
| 13        | TCO     | Mongrel dogs in Tunisia and Turkey | - dogs under 3 months (5% to 20% in Tunisia)  
- dogs accessible to vaccination by mobile vaccination (Tunisia 75% to 85% and Turkey 50% to 60%) and door to door (Tunisia 75% to 85% and Turkey 57%)  
- ownerless dogs account for 6% to 13% in Tunisia and 8% in Turkey |
| 12        | TCO     | >1,300 owned village dogs Tchad | - high vaccination coverage achieved, 88%, or 87% taking into account small number of unowned dogs  
- main difficulties: maintenance of cold chain, lack of time, transport of dogs to vaccination point, dogs too old, too young, sick, or escaped |

RFFIT: rapid fluorescence focus inhibition test  
TCO: tissue culture origin  
VNA: virus-neutralising antibodies

**Other good vaccination campaign practices**

The Tierkel postulate, according to which canine and human rabies can be controlled if about 70% of the dogs in a population are vaccinated, still appears valid (15).

In successful rabies elimination programmes, governments recognise rabies as a major problem and provide for an appropriate cross-sectorial legislative framework, sustainable funds and rabies capacities that are not altered when disease priorities shift (19). Dog vaccination coverage can be further improved by increasing dog owner compliance through comprehensive information campaigns and by adapting campaign logistics to field conditions and local customs (6, 10).

**Conclusions and recommendations**

Understanding the ecological parameters of the dog population is as fundamental to the design and implementation of successful, cost-efficient and sustainable canine rabies control programmes as proper diagnostics and adequate intervention follow-up. A large majority of dogs are accessible to parenteral vaccination in the field and should be vaccinated annually (with 3Y DOI vaccines), regardless of their age, size, breed or sex, to avoid a drop below the herd immunity threshold due to rapid population turnover. Good-quality, cell-culture-derived, parenteral rabies vaccines should be used and conditions of storage and transport that may adversely affect vaccine potency should be avoided. Before oral vaccine for dogs can be used routinely, more research should be conducted.

Finally, while limited removal of unwanted and high-risk dogs can be useful in the context of rabies control, non-selective elimination of dogs, particularly if they have been vaccinated, is not recommended.

**References**


Immuocontraception as a tool for rabies and canine population management

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Summary

Appropriate animal management is crucial in the control of neglected zoonoses, including rabies. Experience has demonstrated significant ecological, economic and ethical limitations to lethal population reduction of rabies virus reservoirs, including dogs. Consistent strategic use of pure, potent, safe and efficacious vaccines results in elimination of canine rabies. Development of novel tools for burgeoning canine populations could simplify attempts at vaccinating against rabies, broadening herd immunity, altering animal reproduction and gaining broader public acceptability. One product, GonaCon™, incorporating adjuvant and gonadotropin-releasing hormone (GnRH), has been used as an immunocontraceptive in mammals, including dogs. As a preliminary evaluation of dual contraceptive-rabies vaccines, the effects of GonaCon on rabies-virus-neutralising antibody induction has been evaluated via its co-administration with commercial rabies vaccine in dogs. Combined use of GonaCon and vaccine did not affect canine anti-rabies virus seroconversion. Given these results, using reverse genetics, GnRH coding sequences were inserted within the Evelyn-Rokitnicki-Abelseth (ERA) rabies virus glycoprotein (G) gene. The amino terminus (N), antigenic site Ila, and junctions between the ecto- and cytoplasmic domains (C) of the G gene were found suitable for GnRH insertion. Rescued recombinant viruses, ERA-N-GnRH and ERA-C-GnRH, replicated as well as parental virus. Expression of GnRH appeared stable in recombinant viruses after multiple cell passages. To increase immunogenicity, two copies of GnRH, aligned in tandem, were fused to the N terminus of rabies virus G. Recombinant viruses reacted with serum from GonaCon-immunised animals. All GnRH-recombinant viruses induced antibodies against GnRH in mice, and protected vaccinated animals against rabies virus challenge. Significantly, fecundity in ERA-2GnRH-vaccinated mice was reduced to 20%, in contrast to 90% conception in unvaccinated controls. By inference, these data should extrapolate to other mammals, including dogs. Besides focused community education efforts about responsible animal ownership, the development of biologics that contain contraceptive and rabies virus antigens may provide substantive enhancement in disease prevention and population control.

Keywords

Introduction

Free-roaming dogs are found throughout the developed and the developing world, creating concerns about their combined impact on public, agricultural and wildlife health (35). Rather than simple, discrete populations of well-managed owned and stray un-owned dogs, the population biology and community ecology of dogs is complex (Fig. 1). Millions of healthy dogs are killed each year in an attempt to decrease their numbers. Currently, surgery is the primary method for permanent companion animal contraception. Although surgical sterilisation prevents dog reproduction, its use is still limited by cost and the availability of competent veterinary services (18). In many parts of the world, perceived problems associated with dog overpopulation are frequently dealt with by lethal control, which at best has only a transient impact on populations. In contrast, some focused projections on applied sterilisation of community dogs have decreased their populations, improved their welfare, and diminished negative impacts on society (55, 60). Ideally, rabies control should rely on mass vaccination of free-roaming, private and community-owned dogs, and not on inefficient killing (65). Because animal welfare, veterinary public health and environmental protection are intrinsically interconnected and improved by public health programmes, it is imperative to develop techniques that are capable of efficiently delivering rabies and population control on a broad scale, with minimal technical requirements and costs (17).

Dog sub-populations: a challenge to achieving sustainable management

Fig. 1
Schematic consideration of different canine populations for targeted management

Obviously, current methods of canine population control are much less than ideal in developed and developing countries alike. Traditional lethal control programmes are often illegal, unwise, unsafe, unethical, expensive, ineffective and publicly unacceptable. In response, ‘collars, not culling’, is becoming a catchphrase of animal welfare organisations, towards a more holistic approach
Scientific advances: current and future tools available for rabies control

involving dog vaccination, responsible pet ownership and population management. Surgical sterilisation is an effective, permanent non-lethal population control method, but is quite limited in scope because of economic and logistical concerns. At least one survey and resulting mathematical population flow model in New York State indicated that euthanasia of unwanted dogs was achievable at a cost below the amount that the average resident was willing to pay to solve the problem (12). Optimal treatment options encompassed both early spay/neuter education plans and low-cost spay/neuter programmes as among the most effective long-term policies, as opposed to other suggestions, such as increased taxes or shelter space. However, the extended universal theory of 'no kill' shelters is often counter-productive in practice and not sustainable, especially under developing country conditions. Typically, older methods of chemical contraception lacked specificity and were often accompanied by numerous adverse events. For future applications, more specific and novel methods of contraception appear necessary.

Immucontraception is a technique employing a generated host immune response to self antigens to interfere with fertility (Table I). The concept is not new (58). The approach was proposed in the early part of the 20th Century, but active research began in earnest only after the pioneering work on chemical contraception during the 1960s, related in part to a basic understanding of auto-immunity and human infertility.

Immucontraception has the potential to be a more practical, cost-effective method of management than traditional spay-neuter programmes. Surprisingly, in many respects, the basic use of immunocontraception in wildlife has outpaced such applications in domestic species. For example, success to date has been achieved in more than 85 different wildlife taxa, at the individual animal and population level (27). Such progress has been achieved particularly in the management of wild horses, deer, bison and elephants (10, 26, 42, 57). Similar challenges faced in the development and application of wildlife contraceptive vaccines are also applicable to free-ranging dogs, including differences in efficacy by target, safety during pregnancy, need for novel delivery systems and constraints of non-contraceptive effects on behaviour. Key functional characteristics of an ideal immunocontraceptive vaccine for dogs include a wide margin of safety, rapid onset, long duration in both sexes across ages, sex hormone inhibition, environmental stability, potential for remote delivery, and low cost, as discussed for other domestic animals and wildlife (27, 31).

Table I
Comparison of various immunocontraceptive vaccine responses in animals

<table>
<thead>
<tr>
<th>Immunocontraceptive gene</th>
<th>Target animal sex</th>
<th>Vaccine construct</th>
<th>Antibody induction</th>
<th>Animal litter reduction</th>
<th>Animal contraception</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pig zona pellucida (PZP)</td>
<td>Female</td>
<td>Pig ovary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>34</td>
</tr>
<tr>
<td>Zona pellucida glycoprotein 3 (ZP3)</td>
<td>Female</td>
<td>Purified ZP3, from pig ovaries or recombinant ZP3 protein</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>40, 41, 69</td>
</tr>
<tr>
<td>ZP3</td>
<td>Female</td>
<td>Recombinant viruses</td>
<td>+/−</td>
<td>?</td>
<td>?</td>
<td>56</td>
</tr>
<tr>
<td>ZP3</td>
<td>Female</td>
<td>Plasmid DNA vaccine</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>52</td>
</tr>
<tr>
<td>ZP3 peptide</td>
<td>Female</td>
<td>Carrier protein conjugated ZP3, or VLP ZP3</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>37</td>
</tr>
<tr>
<td>GnRH</td>
<td>Female and male</td>
<td>Carrier protein conjugated GnRH</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>41</td>
</tr>
</tbody>
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Scientific advances: current and future tools available for rabies control

Table I (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Female and male</th>
<th>Recombinant rabies virus-GnRH</th>
<th>Plasmid DNA</th>
<th>Carrier protein conjugated YLP12 or VLP-YLP12</th>
<th>+</th>
<th>+</th>
<th>?</th>
<th>?</th>
<th>+</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH</td>
<td>Female and male</td>
<td>Plasmid DNA</td>
<td>?</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>YLP12</td>
<td>Female</td>
<td>Carrier protein conjugated YLP12 or VLP-YLP12</td>
<td>+</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Porcine zona pellucida (PZP) obtained from swine ovaries, as a rudimentary mixture, may work well in some females for contraception, but results in ovarian pathology in some species after administration. Purified zona pellucida glycoprotein (ZP3) from swine ovaries does not work as well as PZP.

VLP: virus-like particle
GnRH: Gonadotropin-releasing hormone
YLP12: a 12 amino-acid-long peptide used as a sperm receptor
? : the results are not always consistent in different animal species
+ : positive result
– : negative result

Fig. 2
Selected examples of common reproductive targets for immunocontraception

There are several potential gross targets for a contraceptive methodology (Fig. 2). Many molecules that are both essential and pregnancy-specific can provide potential targets for contraception. In one recent review, at least 76 different critical factors (e.g. cytokines, chemokines, growth factors, etc.) were identified as involved in various steps of the establishment of pregnancy (30).
Focusing upon domestic carnivores, ovarian follicles begin development with each oestrous cycle (47, 49). Follicular development is promoted by the gonadotropin-releasing hormone (GnRH) in the hypothalamus, and its subsequent effect upon the pituitary, with release of follicle-stimulating hormone (FSH) and luteinising hormone (LH). As the follicles develop, estrogen is secreted, with signs of pro-oestrus. In dogs, estrogen concentrations decrease after pro-oestrus, LH results in ovulation, and acceptance of the male by the bitch for breeding. The ovum is released from the follicle into the uterine tube, where fertilisation occurs. The egg is surrounded by a zona pellucida (ZP) and a layer of cumulus cells. Sperm introduced into the reproductive tract undergo capacitation, consisting of an acrosome reaction and acquisition of hypermotility. Capacitated sperm bind to the epithelium of the uterine tube until ova are present. Sperm bind to one of the ZP glycoproteins, permitting cross-linking and fusion with other proteins and a block to polyspermy, as soon as one sperm accesses the inner layer of the ZP.

The ZP was one of the first successful targets for fertility control in animals. To date, the ZP has been used successfully in multiple species, including dogs (15). The ZP is made of up three glycosylated proteins that are highly conserved between species. The abundance of pig ovaries available at abattoirs made porcine ZP (pZP) a popular candidate for vaccine development. However, pZP does not cause a uniform immune response in all species (31). Researchers tried ZP from other species and have seen unpredictable responses after injection, with variable binding of antibodies formed to reproductive tract tissues. Vaccines using pZP in dogs may cause erratic oestrous cycling and may not consistently prevent pregnancy in the long term. For example, vaccines using recombinant canine ZP proteins conjugated to diphtheria toxin in dogs caused a rise in titres and inhibition of ovarian follicular development but did not prevent oestrous cycling and pregnancy in all cases (15). Most ZP vaccine studies in dogs report at least short-term infertility but some were associated with prolonged pro-oestrus bleeding, oestrous behaviour, and ovarian cystic disease.

Based upon comparative research to date, if safe, potent and long-acting immunocontraceptive vaccines were developed, these could provide powerful tools for carnivore population management (31). Arguably, besides the ZP, the GnRH is one contraceptive target that meets the criteria of an ideal vaccine, a ‘master hormone’ that controls reproduction at the level of the hypothalamus. In a functional feedback loop, the GnRH produced in the hypothalamus binds to receptors on pituitary gonadotroph cells, which in turn release LH and FSH. The LH and FSH bind to receptors on the gonads to stimulate estrogen release by the ovaries and testosterone release by the testicles. The basic idea of a GnRH immunocontraceptive product is based upon the binding of generated host antibodies to GnRH and consequent blocking of function. Antibodies directed against GnRH would prevent the normal cascade of hormone secretion required for regulating sexual behaviour and fertility. Hence, GnRH is a candidate to focus upon for canine immunocontraception, because a single product should be effective in both sexes of different ages. Furthermore, because sex hormones can result in some undesirable behaviours (i.e. aggression, wandering, etc.), and adverse health events (i.e. prostatic hypertrophy, mammary neoplasia, uterine infections, etc.), blockage of sex hormone production may offer additional health advantages.

The basic concept of using GnRH as an immunocontraceptive product has been confirmed in various species in both sexes by many investigators (6, 7, 9, 19, 22, 28, 33, 44, 52, 62). Neither serious systemic effects nor unusual behavioural changes have been observed in immunised animals to date using such biologics. However, while previous studies of such GnRH products have shown promising results, typically these have required multiple doses of vaccine (20, 29).
Attempts to develop GnRH vaccines for immunocontraception in various wildlife species have been undertaken at the United States Department of Agriculture (USDA) National Wildlife Research Center. As GnRH is a small decapeptide that is not normally immunogenic, multimers of a larger foreign protein (usually keyhole limpet haemocyanin [KLH] or blue protein [Choncolepas choncolepas]) were coupled to synthetic GnRH. This GnRH-KLH conjugate was then combined with an adjuvant (AdjuVac®), composed of an emulsion of mineral oil and Mycobacterium avium from a USDA-licensed Johne’s disease vaccine. The resulting vaccine (GonaCon™) appeared to suppress hormone production and pregnancy following intramuscular administration in many species, including dogs, white-tailed deer, elk, wild horses, swine, bison, cats, California ground squirrels, gray squirrels, prairie dogs and Norway rats (14, 23, 24, 25, 32, 39, 42, 43).

Based in part upon the progress shown in prior research, a recent study was conducted in captive dogs in the Navajo Nation in Arizona, to test for potential interference between GonaCon and a commercial rabies virus vaccine (2). In that study, three groups of six dogs each were administered: GonaCon only; Pfizer Defensor 3 (rabies vaccine) only; or GonaCon and Defensor 3 rabies vaccine at the same time, intramuscularly (IM). The use of GonaCon did not affect the ability of dogs to develop virus-neutralising antibodies to the rabies virus vaccine. However, neither breeding studies nor rabies virus challenge tests were conducted during this small preliminary study. Clinical chemistry health profiles were performed pre- and post-vaccination, and values were not significantly different, demonstrating no adverse health effects from the vaccines. Some dogs vaccinated with GonaCon did develop injection site reactions, unrelated to the antibody response. This original GonaCon formulation may cause local injection site reactions in some animals (38). Such reactions may be caused in part by an immunological response, due to cross-reactivity with other vaccinations (e.g. leptospirosis) typically administered to domestic dogs.

The primary development of such GnRH vaccines as GonaCon for domestic animals and wildlife, and subsequent experimental use in dogs, prompted additional interest for combined potential use in rabies control (36). While promising in small-scale studies, the potential drawbacks of a GnRH-conjugate/adjuvant concept for more widespread application in developing countries include the economics of peptide synthesis and the relatively large size of the molecules needed to be produced. Generally, peptide synthesis by chemical methods is fairly costly and difficult for large-scale production. Also, such large conjugated molecules cannot be processed easily on mucosal surfaces and would have to be administered parenterally, such as via the IM route. As ‘self antigens’, conjugates are probably necessary for the induction of adequate immune responses, and the need for conventional adjuvants and potential for adverse effects, such as injection site masses, is a concern when employing a traditional approach to developing immunocontraceptive vaccines (32, 48). For this reason, some researchers have considered the use of viral vectors to overcome the resistance to ‘self antigens’ (16, 45).

Replicating live, attenuated, vector vaccines may produce longer-lasting immune responses through copy multiplication compared to peptide/protein approaches, such as GnRH (which has a limited biological half-life in circulation). For example, yellow fever virus-neutralising antibodies persist for ~30–35 years after immunisation (50). Smallpox vaccine provides immunity in humans for at least ten years after a single vaccination (1). Hence, the limitations of peptide administration alone may be overcome by viral vaccine copy multiplication (20, 70, 71). As such, an ideal GnRH peptide could be presented as multiple copies on the surface of a viral vector, especially if it possesses strong B- and T-cell epitopes. Such constructs could enhance an immunocontraceptive response, simplify the manufacturing process and eliminate the need for an adjuvant, which is otherwise essential when a small target protein product such as GnRH is used alone. Moreover, recombinant

Compendium of the OIE Global Conference on Rabies Control
immunocontraceptive rabies vaccines could reduce clinical visits and provide dual rabies vaccination and contraception in both sexes. The cost of production and administration would be reduced for a single biologic, rather than two separate vaccines given individually, one for rabies and one for contraception. Additionally, an immunocontraceptive rabies vaccine could save time for veterinarians and programme managers by providing concomitant immunisation.

To this effect, rabies virus has been used for molecular engineering, selecting the Evelyn-Rokitnicki-Abelseth (ERA) strain, which has been proven immunogenic, safe and efficacious in field settings for more than 30 years (11). Considering its historical use as a seed virus, such a recombinant ERA viral vaccine could be easily and cost-effectively produced on a large scale, if engineering does not alter replication capability. Recombinant rabies virus was engineered using reverse-genetics techniques, recovered and grown to high virus titres in BSR cells (66, 67). Different locations in the rabies virus glycoprotein were identified for insertion of the intended foreign products (Fig. 3). The N terminus of the glycoprotein has the capacity to accept multiple copies of the target GnRH. Approximately 3,000 copies of the GnRH are usually presented on each rabies virion. Recombinant rabies viruses carrying multiple copies of foreign genes can replicate up to $1 \times 10^9$ focus-forming units per ml in cell culture, making large-scale production of recombinant viruses feasible for commercial consideration.

The GnRH could be detected on the infected cell surface, co-localised with rabies virus glycoprotein. In preliminary experiments, three-week-old mice inoculated with selected recombinant viruses showed no signs of rabies, and demonstrated high titres of rabies virus-neutralising antibodies approximately three weeks post-administration. All mice survived challenge with a lethal dose of street rabies virus. In addition, in one contraception experiment, only 20% of vaccinated mice became pregnant, compared to 90% of controls (68). These preliminary studies are very encouraging, prompting the need for proof-of-concept research in dogs.

**Fig. 3**

*Fusion of gonadotropin-releasing hormone peptide to rabies virus ERA glycoprotein*
Note: Fusion of the gonadotropin-releasing hormone (GnRH) copies into the glycoprotein gene of the rabies virus ERA strain and viral growth curves of the recombinant viruses were compared (arrows mark positions of the rabies virus glycoprotein tested for insertion of GnRH; red arrows indicate sites suitable for insertion of one copy of GnRH). The N terminus of the glycoprotein between the signal sequence (SP) and ectodomain (ecto-) was selected for insertion of multiple copies of the GnRH, rather than the trans-membrane or TM domain. Northern blot analysis indicated expression of the glycoprotein is not affected by insertion of GnRH (lanes 1 and 4: RNA molecular markers, size given in nucleotides, lanes 2 and 3: RNA extracted from ERA-N-GnRH and ERA-N-2GnRH). Similarly, the growth of the ERA rabies virus strain was not affected by insertion of GnRH at the N terminus of the glycoprotein.

Selection of the ERA rabies virus strain was deliberate, given its historical usefulness as a parenteral veterinary vaccine, as well as its use for oral wildlife vaccination. For example, during mass immunisation campaigns against rabies, either door-to-door or through centralised vaccination clinics, dogs could be vaccinated by the IM or subcutaneous routes, as occurs now, using traditional commercial vaccines. Moreover, for less tractable or free-ranging community dogs that may prove more challenging to restrain and immunise by hand, the use of vaccine-laden baits could be employed (3). As opposed to the strategic distribution of oral vaccines for wildlife by aircraft, dual rabies immunocontraception of dogs could exploit a ‘hand-out’ model to lessen concerns over potential impacts to non-target species from environmental release. Alternatively, if major safety concerns persist and are validated over the use of a replicating rabies immunocontraceptive biologic, various inactivated and adjuvanted techniques could be pursued. Rabies virus-neutralising antibodies induced by modern, inactivated cell culture vaccines can persist in humans for more than ten years, and with efficacy for at least three years in cats and dogs after a single administration (59).

Considering that, as of yet, there are no licensed immuncontraceptive vaccines for domestic dogs, and assuming that potent and efficacious products are actually developed over the next five years, a myriad of related questions remain beyond the basic research issues at hand. For example, what is a desirable canine density for each community, which meets both local societal needs and achieves epidemiologically practical disease control? Is a prime-boost strategy feasible logistically and economically, or should a single vaccine administration be the goal? How frequently should a contraceptive vaccine be used over time in individual dogs to maximise efficacy and minimise the opportunity for tolerance? When would permanent or more flexible, reversible, rotational contraception be more desirable? Will prior immunity from vaccination or infection exhibit an inhibitory effect to dual rabies immunocontraception, based on timing and degree of response? Are surveillance systems in place to detect individual subtle adverse health effects in community dogs after multiple doses? What are the potential long-term ecological effects upon social behaviour and population structure? Would geographic or breed-specific effects be operative? What would be the biosafety recommendations after accidental human exposures? How should such products be considered in the regulatory environment? If used as a dual, reverse-genetics virus component, should the primary focus be upon purity, potency, safety and efficacy in regard to the rabies virus component (as pregnancy is not regarded traditionally as a ‘disease’, and contraception might not be claimed on a product but viewed rather as a side effect in post-marketing surveillance)?

For immunocontraceptives to gain a more prominent role in dog population management than intrusive and less socially palatable methods, they must be safe, immunologically effective, inexpensive to produce, and capable of being delivered at low cost to the target segment of the dog population. In areas where free-roaming individuals make up a substantial proportion of the total dog population, oral delivery may take on an added importance to efficiently reach thresholds of herd immunity to achieve canine rabies elimination. In addition, although social behaviour and structure can be determinants of mating success, domestic dogs tend to be promiscuous (8, 63). Nevertheless, dog abundance can be expected to be driven largely by reproductively competent bitches within a population. GonaCon has been demonstrated as an effective immunocontraceptive in both sexes of several species evaluated (39, 42, 43). However, an appreciable reduction in fecundity and relative
dog abundance may be best achieved through strategies that ensure sufficient numbers of bitches receive immunocontraceptive vaccines, either parenterally or orally. Ancillary benefits may accrue from contraception in males as a result of less roaming for mates, and lower aggression due to suppressed testosterone production. Recently, GonaCon has been tested in captive bitches in Mexico (61). Other similar studies are in the planning stages that are expected to include long-term monitoring of vaccinated animals throughout their breeding cycles. Assuming favourable science-based evidence from recent and future studies with GonaCon, it may become one of the first injectable immunocontraceptive vaccines available for integration into canine rabies management programmes. Additional vaccine research and development will be necessary to fulfil the promise of oral delivery as a logical future goal.

Although immunocontraception may hold great value, it is neither a panacea nor will it be a replacement for responsible pet ownership. As demonstrated for some conspecific equid populations, the specific habitat, resources, demographic and eco-physiological variables among different species populations may affect their responses to contraception, and such counter-intuitive, long-term secondary consequences need to be considered (46). Moreover, while it seems intuitive that, for density-dependent diseases, pathogen transmission rates should fall with the decreased numbers of progeny after contraception, and with fewer interactions, given fewer sexually driven encounters, confirmatory data are often lacking (21, 64).

**Recommendations**

Clearly, this is an exciting and challenging opportunity for a broad spectrum of scientists and policy-makers to embark upon the duality of managing both diseases and populations of domestic and wild, owned and free-ranging animals, and to probe the intriguing quantitative effects that reduced sexual reproduction and fertility might exert on other animal behaviours, social organisation and, ultimately, evolutionary biology (13). Hence, the generation of baseline ecological data and modelling of comparative demographic parameters of dogs in different environments are of fundamental importance now, before the advent of such 21st Century biologics in actual rabies prevention and control activities.

**Acknowledgements**

The authors thank the staff members in their programmes and their colleagues abroad for their crucial contributions thus far on this important research and management topic. The use of brand product names is for comparison purposes only and does not constitute endorsement by the United States government.

The views expressed in this communication are those of the authors and do not necessarily reflect those of their host institutions.

**References**


**Canine adenovirus antibodies in meso-carnivores in the United States of America: implications for oral rabies vaccination using recombinant adenovirus vaccines?**


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**Summary**

A recombinant canine adenovirus (serotype 2) rabies glycoprotein vaccine (CAV2-RG) has demonstrated efficacy in protecting against rabies in captive striped skunks and raccoons. In addition, the vector for this vaccine is unlikely to pose potential public health concerns such as those associated with other recombinant oral rabies vaccines currently in use in North America. In preparing to evaluate CAV2-RG as a prospective candidate for field testing, we conducted serological surveys representing a diverse range of meso-carnivore rabies reservoir species in North America to determine baseline CAV virus-neutralising antibodies (VNA). Of the 1,128 animals included in this analysis, 22.7% (n = 256) tested positive for CAV VNA. This CAV VNA presence differed among species (P < 0.05), and was the lowest among raccoons (Procyon lotor) (3.4%, n = 610) and highest among coyotes (Canis latrans) (78.4%, n =116). Similar (P > 0.05) intermediate CAV VNA activity was observed in the small Asian mongoose (Herpestes javanicus) (27.1%, n = 85), striped skunk (Mephitis mephitis) (37.3%, n = 201), and gray fox (Urocyon cinereoargenteus) (39.7%, n = 116). No CAV VNA was detected in mongoose samples from Hawaii (n = 31, 2011), but a 42.6% (n = 54) presence was observed in Puerto Rico. These findings suggest that meso-carnivores more distant phylogenetically from Canis species would probably respond more favourably to field application of CAV2-RG presented in a proper bait formulation. However, due to background CAV VNA levels, CAV2-RG may not be expected to be equally effective in oral rabies vaccination campaigns in all meso-carnivore rabies reservoir species in North America, irrespective of bait formulation. This limitation, together with the current economic climate and other limiting factors, underscores the need for access to a single, safe, inexpensive oral rabies vaccine in the United States that is efficacious in all meso-carnivore rabies reservoir species.
Keywords


Introduction

In the United States (USA), oral rabies vaccination (ORV) campaigns are directed:

– at canine rabies in coyotes (Canis latrans) in southern Texas, where the disease had spilled over from rabid dogs (Canis lupus familiaris) in Mexico

– unique rabies virus variants in grey foxes (Urocyon cinereoargenteus) in Texas and Arizona, and

– raccoon (Procyon lotor) rabies in the eastern USA.

Through the successful integration of ORV into conventional rabies prevention and control, the USA was declared free from dog-mediated rabies in 2007 (12). Since May 2009, ORV campaigns have resulted in no reported grey fox rabies cases in Texas (2); reduced grey fox cases to near zero near Flagstaff, Arizona; and have prevented appreciable spread of raccoon rabies in the eastern USA (9).

In spite of these accomplishments, there are several additional known meso-carnivore rabies reservoirs in the USA and its territories (2). Among these, the striped skunk (Mephitis mephitis) plays a significant role in the epidemiology of wildlife-mediated rabies; distinct variants of rabies virus in the striped skunk collectively occupy the broadest geographic area in the USA (2). The striped skunk appears the most refractory to oral rabies vaccination in the field. Meaningful levels of vaccine-induced antibodies have not been observed in skunks in areas where multiple ORV campaigns targeting raccoon rabies with Raboral V-RG® (Merial Ltd, Athens, Georgia, USA) have occurred (6, 10). The most immediate concerns, therefore, are access to a more effective oral vaccine bait for raccoon rabies control, including the ability to address frequent spillover of raccoon rabies virus into skunk populations. Spillover represents an opportunity for maintenance of this variant by skunks (4) that could serve as an impediment to achieving raccoon rabies management goals.

Positive results from studies of a recombinant canine adenovirus (serotype 2) rabies glycoprotein vaccine (CAV2-RG) in laboratory mice (6) led to captive studies that demonstrated immunogenicity in skunks and raccoons delivered per os (5). In light of these early results, and the reduced human health risks associated with CAV2 vector for expressing the rabies virus glycoprotein, in comparison to other recombinant oral rabies vaccines currently used in North America, expanded field serological surveys were conducted to determine background CAV virus-neutralising antibodies (VNA) in wild caught coyotes, grey foxes, small Asian mongooses (Herpestes javanicus), raccoons and striped skunks from 12 states and Puerto Rico.

Methods

Excess sera collected during sampling of wild meso-carnivores from 2001 to 2011 by the US Department of Agriculture Wildlife Services and the Texas Department of State Health Services to evaluate ORV campaigns in coyotes, grey foxes, raccoons and skunks, which had been stored in labelled cryovials at –60°C to –70°C, were provided to the Animal Health Diagnostic Center, Cornell University, New York, on dry ice via overnight mail for serological analysis. Frozen mongoose sera were also provided on dry ice that had been collected from Hawaii and Puerto Rico, specifically for CAV VNA analysis and other disease surveillance.
A canine adenovirus serotype 1 (CAV1; infectious canine hepatitis) VNA assay was used following standard procedures for VN assays in microtitre plates. Two-fold serum dilutions (50 ul) in duplicate were mixed with 100 to 300 median tissue culture infective doses (TCID$_{50}$) of CAV1 (Baker Institute, Cornell University) in a 50 ul volume. Mixtures were allowed to incubate for at least one hour at room temperature. A 100 ul volume of indicator cells (Madin-Darby canine kidney [MDCK]) was added to each well and the plates were placed in a CO$_2$ incubator at 37°C for four days. Wells were scored for the presence or absence of typical CAV1 cytopathology. The CAV VNA values were determined as titres (reciprocal of end-point dilution). The calculation used serum dilutions with a 50% end-point determination. Titres of four or greater were considered positive (1, 3).

We conducted Fisher’s exact tests to determine whether species differed in their CAV VNA presence. We conducted a multiple logistic regression to analyse potential relationships between the presence of CAV VNA for year, state, species, relative age and sex. Because no CAV VNAs were detected in mongoose samples from Hawaii but were present in Puerto Rico, this difference was evaluated with Fisher’s exact test. All statistical analyses were conducted in SAS 9.1 (2002, SAS Institute, Cary, North Carolina).

**Results**

Sera from 1,128 wild-caught coyotes, grey foxes, small Asian mongooses, raccoons and striped skunks from 12 states and Puerto Rico (from 2001 to 2011) were analysed for CAV VNA (Table I). A total of 22.7% (256/1,128) animals were positive for CAV VNAs (Table II). The highest CAV VNA presence was found among coyotes (78.4%; $P \leq 2.509$ E-9) and the lowest was among raccoons (3.4%; $P \leq 1.564$ E-11). A similar ($P > 0.0721$) intermediate CAV VNA presence was observed among samples from the small Asian mongooses (27.1%, $n = 85$), striped skunks (37.3%, $n = 201$), and grey foxes (39.7%, $n = 116$) (Table III).

**Table I**

<table>
<thead>
<tr>
<th>State</th>
<th>Coyotes</th>
<th>Grey foxes</th>
<th>Mongooses</th>
<th>Raccoons</th>
<th>Skunks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>17</td>
<td>17</td>
<td>x</td>
<td>x</td>
<td>39</td>
<td>73</td>
</tr>
<tr>
<td>Hawaii</td>
<td>x</td>
<td>x</td>
<td>31</td>
<td>x</td>
<td>x</td>
<td>31</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Maryland</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>102</td>
<td>x</td>
<td>102</td>
</tr>
<tr>
<td>Maine</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>New York</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>121</td>
<td>27</td>
<td>148</td>
</tr>
<tr>
<td>Ohio</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>126</td>
<td>x</td>
<td>126</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>74</td>
<td>x</td>
<td>74</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>x</td>
<td>x</td>
<td>54</td>
<td>x</td>
<td>x</td>
<td>54</td>
</tr>
<tr>
<td>Tennessee</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>38</td>
<td>9</td>
<td>47</td>
</tr>
<tr>
<td>Texas</td>
<td>99</td>
<td>99</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>198</td>
</tr>
<tr>
<td>Vermont</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>113</td>
<td>34</td>
<td>147</td>
</tr>
<tr>
<td>West Virginia</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>36</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>116</strong></td>
<td><strong>116</strong></td>
<td><strong>85</strong></td>
<td><strong>610</strong></td>
<td><strong>201</strong></td>
<td><strong>1,128</strong></td>
</tr>
</tbody>
</table>
### Table II
**Canine adenovirus virus-neutralising antibodies: results from 1,128 wild meso-carnivores in the United States and Puerto Rico, 2001 to 2011**

<table>
<thead>
<tr>
<th>Species</th>
<th>Number tested</th>
<th>Number positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyotes</td>
<td>116</td>
<td>91 (78.4)</td>
</tr>
<tr>
<td>Grey foxes</td>
<td>116</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>Mongooses</td>
<td>85</td>
<td>23 (27.1)</td>
</tr>
<tr>
<td>Raccoons</td>
<td>610</td>
<td>21 (3.4)</td>
</tr>
<tr>
<td>Striped skunks</td>
<td>201</td>
<td>75 (37.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,128</strong></td>
<td><strong>256 (22.7)</strong></td>
</tr>
</tbody>
</table>

### Table III
**Comparison of the presence of canine adenovirus virus 2-neutralising antibodies in various wildlife species in 12 states and Puerto Rico, 2001 to 2011**

<table>
<thead>
<tr>
<th>Wildlife Species</th>
<th>Comparison</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyotes vs Grey foxes</td>
<td>x, P = 2.509 E-9</td>
<td></td>
</tr>
<tr>
<td>Coyotes vs Mongooses</td>
<td>x, P = 4.092 E-13</td>
<td></td>
</tr>
<tr>
<td>Coyotes vs Raccoons</td>
<td>x, P = 4.375 E-71</td>
<td></td>
</tr>
<tr>
<td>Coyotes vs Striped skunks</td>
<td>x, P = 1.011 E-12</td>
<td></td>
</tr>
<tr>
<td>Grey foxes vs Mongooses</td>
<td>x, P = 0.0721</td>
<td></td>
</tr>
<tr>
<td>Grey foxes vs Raccoons</td>
<td>x, P = 4.09 E-25</td>
<td></td>
</tr>
<tr>
<td>Grey foxes vs Striped skunks</td>
<td>x, P = 0.7194</td>
<td></td>
</tr>
<tr>
<td>Mongooses vs Raccoons</td>
<td>x, P = 1.564 E-11</td>
<td></td>
</tr>
<tr>
<td>Mongooses vs Striped skunks</td>
<td>x, P = 0.1033</td>
<td></td>
</tr>
<tr>
<td>Raccoons vs Striped skunks</td>
<td>x, P = 2.308 E-32</td>
<td></td>
</tr>
</tbody>
</table>

No CAV VNA was detected in mongooses in Hawaii (n = 31), while 42.6% (n = 54) of mongooses in Puerto Rico were CAV VNA-positive (P = 5.155 E-06).

The CAV VNA presence was significantly higher in grey foxes sampled from Texas (47.8%, n = 99) than in those from Arizona (21.4%, n = 17) (P = 0.0319). Skunk samples from 2009 had a higher (P = 0.0485) (68.2%, n = 22) CAV VNA presence than in other years in which samples were available for testing (2005 to 2008) (Tables IV and V). No other variables evaluated were significant (P > 0.05).

### Table IV
**Multiple logistic regression of potential factors affecting the presence of canine adenovirus virus-neutralising antibodies in four meso-carnivore species in the United States and Puerto Rico, 2001 to 2011**

<table>
<thead>
<tr>
<th>Species</th>
<th>Variables (Wald Chi-square, degrees of freedom, P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coyotes</td>
<td>Year 4.8349, 6, 0.5652 State 0.8614, 1, 0.3533 Relative age 0.1324, 2, 0.9359 Sex 0.8613, 1, 0.3534</td>
</tr>
<tr>
<td>Grey foxes</td>
<td>Year 3.5886, 5, 0.6100 State 4.6043, 1, 0.0319 Relative age 0.0027, 1, 0.9586 Sex 0.0027, 2, 0.9986</td>
</tr>
<tr>
<td>Raccoons</td>
<td>Year 2.6886, 2, 0.2607 State 1.7124, 5, 0.8873 Relative age 3.1529, 2, 0.2067 Sex 0.3247, 2, 0.8502</td>
</tr>
<tr>
<td>Skunks</td>
<td>Year 7.8845, 3, 0.0485 State 8.0014, 6, 0.2380 Relative age 0.1745, 2, 0.9164 Sex 1.2812, 2, 0.5270</td>
</tr>
</tbody>
</table>

### Table V
**Canine adenovirus virus-neutralising antibodies in skunks from 2006 to 2009**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number tested</th>
<th>Number positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>74</td>
<td>30 (40.5)</td>
</tr>
<tr>
<td>2007</td>
<td>46</td>
<td>17 (37.0)</td>
</tr>
<tr>
<td>2008</td>
<td>69</td>
<td>20 (29.0)</td>
</tr>
<tr>
<td>2009</td>
<td>12</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>201</strong></td>
<td><strong>75 (37.3)</strong></td>
</tr>
</tbody>
</table>

Samples came from: Arizona, Massachusetts, Maine, New York, Tennessee, Vermont and West Virginia.
Discussion

The issue of cross-protection between CAV1 and CAV2 has been firmly established in domestic dogs and the CAV1 component of earlier, modified live vaccines was replaced by CAV2, due to this strong cross-protection. The serological cross-reactivity of these neutralising antibodies is also well established. However, as measures of protection from infection, neutralising antibodies represent one immune component, given that cell-mediated immunity is often significant in response to exposure to viral pathogens. In wildlife, the evidence for natural CAV2 infections is largely non-existent. The virus circulating in wildlife is CAV1, as this agent was previously known as infectious encephalomyelitis of foxes. In a comparison of 68 wild canid sera tested for CAV1- and CAV2-neutralising antibody titres, the geometric mean titres were not substantially different (CAV1–316; CAV2–277) (E.J. Dubovi, unpublished data). Others have also concluded that it is not possible to distinguish CAV1 infections from CAV2, based on serology (2). Accordingly, we chose to test the wildlife sera with a CAV1 virus to capture all animals exposed to a canine adenovirus and thus those that might resist responding to a CAV2-vectored vaccine, either by neutralising antibodies or cell-mediated mechanisms.

The overarching goal of this study was to provide a serological context from wild meso-carnivores to make an evidence-based decision regarding continued research focused on CAV2-RG for potential use in ORV in the USA, where programmes are in place to control rabies in raccoons, grey foxes and coyotes (8, 9). Since ORV began in the USA in the 1990s, Raboral V-RG® has, to date, been the sole oral rabies vaccine available for use (9). This vaccine remains an important tool for ORV in the USA, but its limitations include difficulty in consistently achieving population immunity levels in raccoons (7) to move towards more aggressive elimination campaigns and it has not produced meaningfully detectable VNA in skunks sampled from ORV zones targeting control of raccoon rabies (9). Frequent spillover of raccoon rabies virus variant into skunks presents a challenge in meeting raccoon rabies goals that ultimately include elimination, given that skunks may play a role in virus maintenance (4). Perhaps more important is an increased risk of viral adaptation and a host shift as a function of frequent spillover of raccoon rabies virus variant into skunks, if intervention with ORV cannot proceed towards the elimination of raccoon rabies in a timely manner.

Low levels of CAV VNA in wild raccoons tested in this study, from broad geographic areas (Table I) where raccoon rabies is present in the eastern USA, suggest that immune interference from existing CAV VNA may not adversely affect the use of CAV2-RG for ORV. At a percentage of 37.3% (n = 201) CAV VNA in the skunks that have been evaluated, there is a suggestion that interference could have a negative effect on population levels of seroconversion if CAV2-RG were used. Although skunk samples were evaluated from seven geographically dispersed states, relatively low sample numbers, ranging from nine in Tennessee to 47 in Maine (Table I), as well as a year effect in 2009, suggest that additional sample evaluation is warranted to better characterise CAV VNA dynamics in skunks. Similar VNA to CAV2 or closely related antigens (e.g. CAV1) were reported for wild-caught raccoons (6%, n = 52, Virginia, 1985) and skunks (32%, n = 22, Illinois, 1984) (11).

A naturally acquired CAV VNA level of 78.4% in coyotes is not surprising, assuming co-evolution with CAV among Canis spp., as well as an active interface with free-roaming domestic and feral dogs as sources of infection in coyotes (8, 12). A similar high CAV VNA was reported from coyote samples (81% in adults and 63% in juveniles, n = 122) collected from south-eastern Colorado, from 1997 to 2001 (3). If these elevated VNA levels are representative of trends in coyotes, they would likely undermine the use of CAV2 as an effective vector for orally vaccinating coyotes. While the CAV seropositivity level of 39.7% was significantly lower in grey foxes, immune interference could also limit its effectiveness in this species. In light of these findings, continued sampling of broader geographic scope and intensity is warranted in coyotes and grey foxes. The documented effectiveness
of Raboral V-RG® in both coyotes and grey foxes in Texas (8) would require compelling data for a shift to occur to a new oral rabies vaccine, such as CAV2-RG.

The absence of CAV VNA in Hawaii (n = 31), and a presence of 42.6% (n = 54) in Puerto Rico, suggests an 'island effect' that could be a function of a higher incidence of interactions with free-roaming and feral dogs in Latin America. High levels of CAV VNA in wild mongooses (77%, n = 30, 1985) have also been reported for Barbados (11). Nevertheless, further investigation would be required to test this hypothesis. Ideally, this would include samples from additional islands that support exotic small Asian mongooses and background information on dog populations. However, research to determine if CAV2-RG is efficacious in the small Asian mongoose would constitute a priority before committing to extensive serological sampling explicitly for this purpose.

While CAV2 virus meets many of the criteria as an ideal vector for a recombinant oral rabies vaccine (5), this study underscores the concern that there is potential for inhibition by naturally occurring VNA, particularly in Canis spp. As such, CAV2-RG, like Raboral V-RG, leaves a void if it cannot effectively vaccinate all meso-carnivore rabies reservoir species in the USA.

**Conclusions**

Based on the presence of CAV VNA in the samples analysed, CAV2-RG delivered in proper baits would be expected to perform well in the raccoon. Assuming inhibition from naturally acquired CAV VNA, CAV2-RG does not appear to be an ideal vector for ORV in coyotes.

Additional samples that represent a greater geographic scope over time should be analysed to better characterise the spatial-temporal CAV VNA dynamics among meso-carnivore rabies reservoir species.

Given the relatively limited ORV market that currently exists in the USA (eight to ten million baits/year) (10), the current economic climate, and other limiting factors, the need remains for a single, safe, inexpensive oral rabies vaccine that is effective in controlling rabies at its source in all meso-carnivore rabies reservoir species in the USA.

**Acknowledgements**

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**References**


Impact of animal rabies on local economy

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Summary

In any country in which rabies is present, livestock and other working animals may become infected with the rabies virus. Livestock are an important source of food and income globally and working animals contribute to livelihoods. This is particularly important in non-industrialised countries. Working animals include cattle, buffalo, horses, donkeys and camels, which are commonly used for ploughing and transportation of people and goods, as well as dogs used for hunting, herding, assisting military and police forces and guarding property. Moreover, in some cultures, the consumption of dog meat is a source of protein and income.

In recent years there has been an increased public recognition of the importance of rabies as a cause of suffering and economic loss; however, the lack of reliable data on rabies is a major constraint to accurately assessing the impact of the disease on local economies. The economic impact of rabies includes direct loss of human and animal life and consequent loss of productivity and labour. Costs incurred to pay for medical diagnosis and treatment, including transportation and post-exposure prophylaxis, are a significant burden on families and communities. The spread of rabies in a community may lead to the emergency sale of production animals and livelihood assets, further affecting these communities’ food and economic security.

The authors call for improved rabies surveillance systems, including outbreak investigations and special epidemiological studies, and improved assessment of the economic and public health effects of rabies on livestock, as well as on local and national economies. This information would make a valuable contribution to raising public awareness of rabies, and help to guide the appropriate allocation of resources to control the disease and reduce its social and economic impact.

Keywords

Introduction

Small-scale livestock farmers and farming communities in developing countries are economically vulnerable groups, for which animal diseases can have devastating consequences. Zoonoses, including rabies, are of particular concern, due to their effects on both the local economy and public health (3). However, accurately estimating the impact of human and canine rabies on society has long been constrained by a lack of epidemiological data. It is even more difficult to accurately assess the impact on economies when rabies affects livestock and working animals. Livestock contribute to local economies worldwide, providing not only food but also non-edible products, such as hides, skin and wool, which are in turn used as raw materials for manufacturing and provide income. In addition, working animals provide draught power for agriculture and transportation, and contribute to financial security. In rural households, dogs are often used for hunting, herding livestock, protecting property, and assisting military and police forces. Consumption of dog meat is a common practice in many cultures, sometimes as a delicacy and sometimes of necessity due to poverty or famine.

The impact of rabies

Rabies has a severe impact on local economies, including human deaths and loss of livestock and working animals. However, there is a need for reliable data collection and analysis to quantify this impact and determine the economic costs and benefits of rabies prevention and control interventions. The currently available models of global rabies prevalence underestimate the incidence of disease; nonetheless, the World Health Organization (WHO) ranks rabies 11th among fatal human infectious diseases, causing an estimated 55,000 human deaths each year (17, 19).

The overall impact of rabies at household, community and local economy levels includes both direct impacts and consequential costs. The most obvious direct impact of rabies is the loss of human and animal life, both of which have profound consequences, especially in rural settings. The death of a family or community member not only leads to the loss of income and labour, but can also result in substantial funeral costs (6). Loss of previously healthy livestock deprives families of an important asset in terms of productivity and income. The loss of a good herding, hunting or guard dog can affect family security. In addition, the exposure of humans to possibly rabid animals can lead to costs associated with seeking medical care, purchasing post-exposure prophylaxis, and productivity lost in caring for family or community members.

The indirect or consequential costs of rabies also need to be considered when assessing the impact of rabies. Preventive vaccination, whether for humans or animals, is an additional cost to be borne due to the disease. Productivity is also lost in some areas simply because rabid animals are present – preventing children from walking to school or farmers going to their fields until the threatening animals are destroyed.

Research suggests that rabies has a low impact on food safety, but the destruction or loss of food animals can have a significant impact on food security. This is particularly true for communities living in extreme poverty. Rabies infection has not been documented to occur by consumption of meat from a rabid animal, although it cannot be excluded (20). The virus can replicate to a limited extent in muscle tissue, but only propagates to high titres in neural tissue and salivary glands. Consequently, it is believed that the most important risk related to the consumption of rabid animals is exposure to infected tissues and saliva through slaughter and handling (12, 16). For this reason, international meat-inspection guidelines require that rabid food animals be condemned and disposed of appropriately. For communities in which dog meat is consumed, the risk of exposure to rabies virus should be assessed. Nevertheless, because the case fatality ratio for rabies is 100%, even low-risk
situations can lead to a costly public health response. For example, in 2008 in Malawi, as many as 1,000 people were exposed to meat from a cow that died of rabies and its meat sold. Post-exposure prophylaxis was administered to 800 people (10).

**Impact of rabies in livestock and working animals**

Rabies can cause a substantial loss of income from the mortality of draught animals or animals used for production as well as for non-food products. According to the 2004 WHO Expert Consultation on Rabies, livestock losses in Africa and Asia are estimated at US$ 12.3 million annually (18). A study that looked at the submission of cattle specimens to central veterinary laboratories in Africa and Asia estimated an annual incidence of 5 deaths/100,000 head of cattle (5). A participatory survey of livestock-keeping communities in Tanzania highlighted rabies as the most important zoonosis in livestock production systems (15). Rabies in cattle is well known in Africa, where livestock may be exposed to rabid dogs and jackals. Rabies is also reported in other species. For example, donkeys are affected by rabies in Mauritania and camel rabies has been reported from Mauritania, Sudan and recently from Uganda (1, 2, 13).

Haematophagous bats (vampire bats) exist only in Latin America, from Mexico to the northern provinces of Argentina, and are a significant reservoir of rabies (9). It is estimated that more than one million cattle die annually from vampire bat-transmitted rabies in Latin America (8), causing a marked economic impact on the livestock industry. Yet, in 2004, only 2,591 cases of rabies were reported in cattle (along with 243 horses and 28 sheep) for the whole of Latin America (11). This is not surprising when we consider that there are also significant constraints to reporting rabies cases in livestock in Latin America. In most countries, farmers must pay for laboratory confirmation and receive no compensation for any animal lost, so they are reluctant to submit samples for laboratory diagnosis. In addition, in extensive livestock-rearing systems, animal deaths due to rabies may be misdiagnosed as intoxication, tetanus or anthrax. Although official reporting is weak, anecdotal reports suggest that there has been an increased incidence of bat-mediated rabies in livestock in Latin America. This has been attributed to changes in land-use patterns (e.g. moving cattle into bat habitats), deforestation and reforestation, as well as changes in climate, which may have caused vampire bats to migrate to new areas. To prevent vampire bat-transmitted rabies in livestock and humans, important decisions must be made. This underscores the need for accurate and affordable laboratory diagnosis offered to farmers so that decision-makers can be informed of risks to human and animal health, and preventive measures taken, possibly including routine vaccination of livestock.

In 2010, European countries reported 7,581 animal rabies cases, of which, 3,271 (43%) were domestic animals. Most of these cases were reported in Eastern European countries (14).

**Rabies surveillance: the challenge**

There are strong indications that rabies is an important and widespread disease of livestock and working animals. The primary challenge in assessing the overall impact of rabies is the lack of reliable data, especially in developing and transition countries. The World Organisation for Animal Health (OIE) and WHO have urged countries to make rabies a notifiable disease and routinely report all cases of rabies in animals and humans yet, at this time, few countries comply. WHO collects rabies data electronically on a yearly basis through ‘Rabnet’, an interactive information system able to generate maps and graphs using human and animal rabies data. However, at this time, the Rabnet website wisely reports: ‘Unfortunately, in the absence of regular (at least annual) data uploading from too many WHO Member States, in order to avoid giving a wrong picture of how much and how widely distributed rabies is in the world, the Rabnet site has been closed until further notice’ (www.who.int/rabies/rabnet/en/). The paucity of data available on-line from international health
organisations is evidence of the need for a concerted worldwide effort to measure rabies incidence, using a ‘One Health’ approach that captures timely data from both human and veterinary medical sources (4).

As we have noted above, there are numerous reasons for rabies not being reported. At the national level, there may be a lack of political will, or financial and human resources. Many individuals and communities do not have confidence that rabies cases will be effectively followed up by the healthcare system, either for animals or humans. Once clinical signs are evident, there is little or nothing that can be done for the patient. In addition, in many countries the cost of laboratory testing is a barrier to the accurate diagnosis and reporting of suspected rabies. In cases where there has been no human exposure, there is even less incentive to have the animal tested or reported. This is especially the case for rabies in livestock and working animals, where farmers see substantial costs and few benefits to confirming a rabies diagnosis.

Poor surveillance and diagnostic capacities result in a lack of reliable data to demonstrate the disease burden and motivate policy-makers to establish rabies control programmes. Without good baseline data it is also difficult to evaluate the impacts of control efforts (7).

Conclusion and way forward

What gets measured gets done. Having accurate, timely and species-specific data on rabies incidence will have a profound effect on our ability to advocate for, plan and evaluate programmes to control rabies worldwide. These data should include suspected and confirmed rabies in livestock and working animals, to help establish a baseline for measuring the impact of rabies on local economies. Accurate, routine rabies data are crucial for enhancing awareness and political will at local and national levels, facilitating the mobilisation of resources, and designing cost-effective prevention strategies.

To enhance surveillance systems and rabies data collection, innovative approaches should be explored, such as social incidence assessment, risk perceptions, economic impact and community intervention options. New technologies, such as mobile phones and digital pens, present new opportunities for real-time data sharing between sectors. Operational research could provide new insights, including options for sustainable and effective rabies prevention and control. All this begins with collecting valid and timely data on rabies.

The Food and Agriculture Organization of the United Nations (FAO) is committed to addressing rabies, to contribute to food security and enhance livelihoods. Together, FAO, the OIE and WHO are committed to addressing rabies at the human-animal-ecosystems interface, and strongly encourage Ministries of Agriculture, Health and the Environment to commit resources to rabies surveillance systems, including routine reporting of human and animal cases, affordable laboratory diagnostics, outbreak investigations (conducted jointly by public health and animal health experts), special epidemiological studies and improved assessment of the economic and public health impacts of rabies on livestock as well as on local and national economies.

References


Cost of national wildlife rabies elimination programmes

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Summary

From the beginning of the oral vaccination campaigns in Germany in 1989, until Germany was officially declared rabies-free in 2008, approximately 77 million baits were sited in the field, costing approximately 74.4 million Euros (€). If the expenses incurred during the early years of rabies control, between 1983 and 1988, are included, the total costs are nearer to € 83.8 million. Between 2000 and 2008, the costs for the required accompanying testing (bait intake, seroconversion, rabies infection) amounted to € 17.4 million. Thus, the total costs incurred reached approximately € 101.2 million, of which around € 34 million were financed by the European Commission.

Keywords


Introduction

The control of rabies is a long-standing tradition in Germany. It was mentioned for the first time in 1880 (3). At that time, rabies was already a notifiable disease with compulsory notification and limited control measures for domestic animals. This lasted until World War II. After World War II, the Act no longer applied only to domestic animals, but primarily to wild animals and, in particular, to foxes. It was only in 1970 that new legislative measures governing the control of sylvatic rabies were introduced in Germany (fumigation of fox dens; intensified culling of foxes). The fumigation was carried out by public bodies. The expenditure of this method, which could in retrospect be called ineffective in terms of rabies elimination, cannot be ascertained from this distance but was probably minor, compared with the costs incurred in the oral immunisation of foxes. To promote the shooting of foxes, in some cases, rewards of up to € 50 for each fox shot were offered.

From 1989 to 1992

As a result of new research in the mid-1970s, aimed at this objective, it was possible for the first time, from 1983 onwards, to draw closer to the goal of eradicating rabies via oral vaccination of foxes. This method of rabies control became practicable in 1989 but was only applied to a limited extent, since vaccine capsules still had to be introduced into chicken heads manually before they could be placed, again manually, in the field. With Decision 89/455/EEC (1), the European Community (EC) took over some of the responsibility for financing rabies control for the first time: the EC contributed 0.5 ECU (approximately € 0.5) per vaccination bait, provided that the vaccine baits were placed over an area of no less than 6,000 square km. In addition, up to 50% of the delivery costs were financed. If baits were delivered on a voluntary basis, up to 10,000 ECU (approximately € 10,000) were contributed for small-scale preservation and conservation measures. The three-year plan introduced by Germany also took into consideration the former third countries, Austria and Czechoslovakia, and the...
former German Democratic Republic (GDR). In the context of this legal framework, which was in place from autumn 1989 until spring 1992:

- a total of 19.6 million vaccine baits were placed in Germany (~ € 21 million)
- a total of 987,000 vaccine baits were placed in Austria (1989–1992; ~ € 1 million)
- a total of 485,600 vaccine baits were placed in Czechoslovakia (1989/1990; ~ € 506,000)
- a total of 1.44 million vaccine baits were placed in the former GDR (1989/1990; ~ € 1.54 million) (Table I).

Table I
**Number of baits laid and costs incurred in Germany, Austria and Czechoslovakia, 1989 to 1992**
Indirect costs are not included, e.g. staff, diagnostic testing, incentives for hunters, facilities for storing, cooling and transporting the baits

<table>
<thead>
<tr>
<th>Year</th>
<th>Germany</th>
<th>Austria</th>
<th>Czechoslovakia</th>
<th>German Democratic Republic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autumn 1989</td>
<td>1.5 million baits</td>
<td>44,000 baits</td>
<td>49,600 baits</td>
<td>40,918 baits</td>
</tr>
<tr>
<td></td>
<td>€ 1.68 million</td>
<td>€ 46.144</td>
<td>€ 52.012</td>
<td>€ 42.912</td>
</tr>
<tr>
<td>1990</td>
<td>3.28 million baits</td>
<td>152,800 baits</td>
<td>436,000 baits</td>
<td>1.43 million baits</td>
</tr>
<tr>
<td></td>
<td>€ 3.84 million</td>
<td>€ 158.766</td>
<td>€ 453.854</td>
<td>€ 1.5 million</td>
</tr>
<tr>
<td>1991</td>
<td>6.67 million baits</td>
<td>328,800 baits</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>€ 7.36 million</td>
<td>€ 331.546</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1992</td>
<td>7.97 million baits</td>
<td>461,600 baits</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>€ 8.32 million</td>
<td>€ 466.612</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Σ</td>
<td>19.42 million baits</td>
<td>987,200 baits</td>
<td>485,600 baits</td>
<td>1.47 million baits</td>
</tr>
<tr>
<td></td>
<td>€ 21 million</td>
<td>€ 1 million</td>
<td>€ 505.866</td>
<td>€ 1.54 million</td>
</tr>
</tbody>
</table>

The year 1993

In 1993, what had become the European Union (EU) did not contribute towards the costs of the rabies elimination programmes implemented in Member States. Nevertheless, Germany continued with the oral vaccination programme of foxes (approximately 8 million baits; costing approximately € 8 million). Once it was possible to produce machine-made vaccine baits from the mid-1980s onwards, large-scale oral immunisation campaigns were launched to control rabies in foxes. For this purpose, specific systems were developed for placing vaccine baits by aeroplane or helicopter, as well as documentation systems, making it possible to detect the position of each individual bait.

From 1994 to 2008

From 1994 onwards, these control measures (purchase of the vaccine baits and delivery) were co-financed by the EU through Decision 90/424/EEC (2), on the basis of a plan submitted by the Member States. A total of 24 million baits (~ € 21 million) were laid in Germany between 1994 and 1996. These costs included delivery and documentation costs in each case.

The former third countries of Poland and the Czech Republic were included in the German plan from 1997 to 2003, with Germany bearing 50% of the costs incurred in these two countries.
A further 50% of this 50% was co-financed by the EU, so that the financing of rabies elimination measures in these two countries was composed of:

- 50% from the country’s own funds
- 25% from German funds
- 25% from EU funds.

(Poland and the Czech Republic acceded to the EU in 2004 and have since submitted their own plans.) Germany placed a total of approximately 26.2 million baits between 1997 and 2003, with the total costs for purchase, delivery and documentation amounting to approximately € 19.2 million. Over the same period, some 8.5 million baits (~€ 3.2 million) were delivered in Poland and some 4 million baits (~€ 0.94 million) in the Czech Republic (Table II). An additional 6.9 million baits were laid from 2004 until the last oral vaccination campaign in the spring of 2008, at a total cost of € 5.2 million. This means that the total costs for purchasing baits, delivery and documentation in Germany alone amounted to approximately € 74.4 million. The total costs for purchasing baits, delivery and documentation rise to approximately € 83.8 million if one includes the expenses incurred during the early years of rabies control (1983 to 1988). This figure does not include the costs for the accompanying tests (from 2000 until 2008: 77,675 tests to prove the bait intake rate, at € 8.2 each; 71,365 tests to prove seroconversion at € 14 each; 714,538 tests to prove rabies infection at € 21.5 each; 9,782 tests to establish the rabies isolates at € 41.6 each).

Table II
Number of baits laid and costs incurred in Germany, Poland and the Czech Republic, 1994 to 2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Germany</th>
<th>Poland</th>
<th>Czech Republic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of baits</td>
<td>Costs in €</td>
<td>No. of baits</td>
</tr>
<tr>
<td>1994</td>
<td>7,316,350</td>
<td>7,511,538.10</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>9,142,140</td>
<td>7,177,495.07</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>7,824,170</td>
<td>6,236,382.25</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>6,217,630</td>
<td>4,810,670.87</td>
<td>2,463,200</td>
</tr>
<tr>
<td>1998</td>
<td>4,624,700</td>
<td>3,622,483.80</td>
<td>2,443,600</td>
</tr>
<tr>
<td>1999</td>
<td>3,418,400</td>
<td>2,725,949.98</td>
<td>687,923</td>
</tr>
<tr>
<td>2000</td>
<td>3,399,200</td>
<td>2,641,541.96</td>
<td>616,778</td>
</tr>
<tr>
<td>2001</td>
<td>3,446,080</td>
<td>2,207,907.28</td>
<td>646,240</td>
</tr>
<tr>
<td>2002</td>
<td>2,859,900</td>
<td>1,873,236.46</td>
<td>1,166,680</td>
</tr>
<tr>
<td>2003</td>
<td>2,177,000</td>
<td>1,373,880.46</td>
<td>548,460</td>
</tr>
<tr>
<td>2004</td>
<td>1,895,455</td>
<td>1,200,000.00</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>2,682,660</td>
<td>1,701,378.04</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1,352,000</td>
<td>867,763.16</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>804,800</td>
<td>1,000,589.64</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>216,000</td>
<td>444,387.22</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>57,376,485</td>
<td>45,395,204.29</td>
<td>8,572,881</td>
</tr>
</tbody>
</table>
The costs for these tests amount to approximately €17.4 million and were financed by the public sector (Table III). The EU only contributed to these costs from 2007 onwards (with €23,237 in 2007; €18,907 in 2008 and €16,512 in 2009).

| Table III |
| Costs for diagnostic tests, 2000 to 2008 |
| No. of tests | Cost per test (€) | Purpose of test | Total costs (€) |
| 77,675 | 8.20 | Proof of bait intake | 636,935.00 |
| 71,365 | 14.00 | Proof of seroconversion | 999,110.00 |
| 714,538 | 21.50 | Proof of infection | 15,362,567.00 |
| 9,782 | 41.60 | Proof of field or vaccine virus | 406,931.20 |
| **∑ 873,360** | | | **17,405,543.20** |

**Conclusion**

The total costs incurred by Germany between 1989 and 2008 for the purchase and delivery of vaccine baits amounted to approximately €83.8 million, while the total costs for the accompanying tests reached approximately €17.4 million. From this overall total of €101.2 million, around €34 million were financed by the EU.

Germany was officially declared free from rabies in 2008. However, serological testing of foxes (for example, animals found dead, or hit on the roads) has continued, to document Germany’s continuing freedom from rabies and to ensure that rabies infections in foxes are detected as early as possible. These costs continue to be incurred and are borne by the public sector. In 2009 and 2010, 32,657 tests were conducted to confirm or rule out rabies infection for €21.5 each (€702,125.50 in all) and 612 tests were carried out to establish rabies isolates for €41.6 each (€25,459.20).

**References**


World Organisation for Animal Health
standards and scientific activities for rabies control

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Summary

Veterinarians are considered key public health stakeholders because of their crucial role in food security and safety, as well as in the control of zoonoses at the animal source, through the creation of a buffer between the diseased animal source and susceptible human beings. Such is the case with rabies.

Through its international standard-setting work, capacity-building programmes, conferences and scientific network, the World Organisation for Animal Health (OIE) supports Veterinary Services around the globe with policy advice and technical assistance for the diagnosis, control and eradication of rabies. An update on recent revisions and new concepts in OIE standards and activities is provided.

Keywords


Introduction

Rabies is one of the oldest-known diseases, occurring primarily in animals, and is at present, the cause of an estimated 55,000 human deaths annually (2). The majority of victims are children, who have been bitten by rabid dogs. Rabies is an infectious disease with one of the highest case-fatality rates, which presents an underestimated and neglected public health problem. As it has little or moderate effect on the livestock industry, Ministries responsible for national Veterinary Services are, regrettably, often reluctant or unable to mobilise sufficient resources to fight rabies at its source. Most cases of rabies occur in developing countries (the disease being under control in most developed countries) and there is significant under-reporting of cases, in both animals and humans. The under-reporting of human rabies has led to the disease failing to attract the attention that it deserves from the international community and donor agencies. Dogs are the main source and transmitters of rabies in developing countries, notably in African and several Asian countries. Controlling rabies in dogs, including stray dogs, is crucial to prevent human deaths worldwide.

The question might well be asked: why, after being known and feared by mankind for more than 4,000 years, does rabies still remain one of the major fatal infectious diseases of humans?
Rabies is intimately linked to the early history of the World Organisation for Animal Health (OIE), and the importance of controlling this public health problem effectively at the animal source was officially recognised as early as 1928. In this year, during the second General Session of the then ‘Office International des Epizooties’ (OIE), the representatives of Veterinary Services around the globe adopted a resolution (4) dedicated to the fight against rabies. Its strong recommendations called for a better commitment from governments for dog-mediated rabies control, including closer collaboration with the public health sector, and international harmonisation in rabies control and eradication at the animal source. This set of recommendations included guiding principles such as: helpful cross-border collaboration in rabies elimination, the duty of veterinarians towards public health impacts of rabies, compulsory registration of owned dogs and the prophylactic killing, or confinement, of rabid and rabies-suspected animals, respectively. Also included within the guiding principles were the conditions for using rabies vaccine in animals, standards of vaccine quality, and regular reporting to the OIE on the epidemiological rabies situation in each country. Many aspects of these guiding principles are still considered valid pillars of today’s strategies in the fight against dog-mediated rabies. Sadly, the first paragraph of the OIE resolution, namely, the outcry for a more active commitment from all governments for rabies control, continues to be only too relevant.

Following the recommendations of two major international conferences on rabies control organised by the OIE (in Kiev in 2005 and in Paris in 2007), the organisation has urged its Member Countries to institute effective and sustainable rabies control programmes (1).

In the Fifth Strategic Plan (2011–2015), the OIE highlights a number of activities that will support the global fight against rabies. It outlines continued work towards strengthening the technical capacities, management, legislation and good governance of Member Countries’ Veterinary Services. These activities will be actioned through the World Animal Health and Welfare Fund, and in collaboration with global partners such as FAO, WHO or regional partners, as well as global, regional and national donors. One of the major new elements of the Fifth Strategic Plan is the enhanced application of the ‘One Health’ concept to reduce the risks of high-impact diseases at the animal–human–ecosystems interface. The contribution of animal health and veterinary public health to food security will thus be strengthened. The OIE will also concentrate on actions that support food security through the reduction of disease in food-producing animals. Dog-mediated rabies is known to occasionally spill over to farm animals and hence may impair animal production in certain regions of the world.

The OIE has also committed its full support to the initiatives of the Global Alliance for Rabies Control (GARC) and encouraged its Member Countries to actively participate in the annual World Rabies Day (28 September each year), launched by GARC in 2007. In September 2011, the OIE strengthened its collaboration with GARC by an exchange of letters. Since then, the OIE has been an active member of the technical branch of GARC, which has developed, among other resources, the ‘Blueprint for canine rabies prevention and control’ (3). This is a Web-based compilation of tools and useful background information for conducting successful rabies control programmes at a local, national or regional level and it is targeted at a large audience.

Rabies situation and challenges of rabies control today

Since its foundation in 1924, one of the main objectives that the OIE has pursued has been to ensure transparency in the global animal disease situation. Member Countries are encouraged to include OIE-listed diseases, such as rabies, within their national legislation as compulsorily notifiable diseases (5). This facilitates the notification of outbreaks in domestic animals, humans (zoonosis) and wildlife.
These data should improve knowledge on the epidemiology of rabies, forming a crucial basis for launching any relevant disease control programme, or to prevent the introduction of the disease into rabies-free areas.

Detailed analyses of animal health reports, submitted during the past three years up to August 2011, by 173 out of 178 OIE Member Countries, reveal the rabies situation: 110 countries stated that rabies has been present in domestic animals in their territory during the past three years. Only 20 countries, which are mainly small islands located in the Asia–Pacific, with some in the Caribbean region, credibly self-declared that rabies has never been present in their territory. Another 31 territories or countries self-declared that they had experienced intermittent rabies outbreaks during the past 25 years, but not in the current reporting year, and in 12 countries the last rabies outbreak occurred more than 25 years ago. For the remaining five OIE Member Countries, no information was available. A detailed geographic overview of the occurrence of rabies is available in Figures 1a and 1b.

**Fig. 1a**
*Rabies occurrence status, as reported for domestic animals (using the latest World Animal Health Information Database reports available)*
Reported infections with European or other bat lyssaviruses were excluded from the analysis

**Fig. 1b**
*Rabies occurrence status, as reported for wildlife (using the latest World Animal Health Information Database reports available)*
Reported infections with European or other bat lyssaviruses were excluded from the analysis
Many rabies-affected countries in Africa and Asia base their statements solely on clinical observations. The clear lack of laboratory-based surveillance that would confirm rabies cases and thus describe the reality in the field (geographical location, seasonal aspects, numbers and species affected) is leading to significant under-reporting of both human and animal cases of this fatal disease. Although improvements have been observed over the years, there are currently only 164 out of 178 OIE Member Countries that have included rabies as a notifiable disease in their veterinary and public health legislation. Nine OIE Member Countries report that rabies is still not a notifiable disease by legislation in their country and an additional five did not provide any information on rabies notification during the last three years. The worldwide situation for compulsory notification of rabies, when it occurs either in domestic animals or in wildlife, is depicted separately in Figures 2a and 2b. In most countries, due to the sometimes limited capacity and occasionally imposed priorities, of Veterinary Services, rabies occurrences or outbreaks in wildlife are reported and notifiable to a lesser extent than those in domestic animals (see Figs 1a and 2b). For practical and economic reasons, the intensity of surveillance conducted in wildlife is usually lower. As a consequence, the epidemiological situation in wildlife, as reported by countries through the World Animal Health Information System (WAHIS), and made accessible via the World Animal Health Information Database (WAHID), needs to be interpreted cautiously.

**Fig. 2a**
*Overview of countries where rabies is a notifiable disease in domestic animals by legislation*
*Rabies is not notifiable in dogs, but it is in selected other species*

**Fig. 2b**
*Overview of countries where rabies is a notifiable disease in wildlife by legislation*
Over and above the geographical extent of the rabies problem, some additional current challenges for rabies prevention and control will be highlighted here:

– many Veterinary Services have to function with increasingly limited budgets and are forced to prioritise farm animal health
– Veterinary Services face increasing commercial and non-commercial movements of animals worldwide (legal and illegal), enhancing the risk of re-introducing rabies to areas where it had been successfully controlled
– there is a new trend of breeding and keeping wild animal species as exotic companion animals, which pose a rabies transmission risk to humans
– countries encounter pressing difficulties in managing stray dog populations
– it is very difficult to sustain control measures for a sufficient period
– inter-sectorial collaboration, using the ‘One Health’ concept, is difficult to implement and too many countries are discouraged by this complexity.

In view of the issues above, it becomes evident that a comprehensive and sustainable rabies control strategy can be prepared only by taking account of stakeholders from across all sectors and administrative levels; for example, public and animal health services, environmental and/or wildlife agencies, police, customs, local authorities, non-governmental organisations and the general public. Furthermore, there might be opportunities to make use of synergies with existing or planned disease control programmes; for example, campaigns targeted at other dog-specific diseases, or disease control programmes initially targeted at livestock only. Included within this could be the potential for sharing communication channels or logistics.

**OIE support to Member Countries and changing international standards**

The OIE is the international standard-setting organisation for animal health and welfare. OIE standards are democratically adopted by all OIE Member Countries. For terrestrial animals, the OIE’s disease control policy is expressed in the *Terrestrial Animal Health Code* (*Terrestrial Code*) and the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*), which are based on the latest science available. These OIE standards promote the use of internationally standardised, accepted definitions and concepts. Implementation of these concepts for disease control programmes promotes harmonisation and equivalence between countries’ national legislation and supports safe international trade and non-commercial movements of animals. OIE standards further promote protection of human health through the control of animal diseases, including zoonoses, given that the contribution of healthy animals to food security is as essential to human health as the protection of humans from zoonoses. Furthermore, the OIE *Terrestrial Code* includes animal welfare recommendations for ethical principles to be applied in trade and animal disease control, such as stray dog population management. The *Terrestrial Manual* promotes the application of standards for diagnostic techniques and vaccines that meet OIE and/or WHO criteria: a fundamental basis for any surveillance activity, and considered key components of any disease control programme. OIE Reference Laboratories and WHO Collaborating Centres for rabies work closely together for the international harmonisation of laboratory methods for diagnosis, and the quality control of vaccines. Additionally, since 2008, the OIE twinning initiative between laboratories (6) and accompanying training programmes have been intensified to improve diagnostic capability in animal health laboratories throughout the world.
Since 2010, under the guidance of the OIE Scientific Commission for Animal Diseases, the OIE Terrestrial Code standards on rabies have been revised to provide guidance on how to control the disease in a step-by-step manner, focusing on the epidemiologically most relevant host species (dogs, cats and captive wild carnivores). The main considerations in updating these standards were:

- in large parts of the world, dogs are the main source of human rabies infection and related rabies mortalities
- there is a high number of non-commercial movements of dogs and cats
- endemic or sporadic rabies in wildlife or stray animals can easily spill over to domestic animals and humans
- immunisation using qualified vaccines is the method of choice for controlling or eliminating the disease
- animal welfare considerations for stray dog population management are now available
- international standards for diagnosing rabies are approved by the OIE and WHO (if applicable)
- aspects of the quality of Veterinary Services or good governance are considered throughout.

The proposed changes in the OIE Terrestrial Code chapter on rabies took into account the change in lyssavirus taxonomy, and the chapter addresses only classical rabies caused by the ‘rabies virus’ (formerly known as rabies virus genotype-1). Bat lyssaviruses would no longer be considered in determining the disease status of a country, and a focus on dog population management was introduced.

The updated chapter (in the section on diagnostic methods) on rabies from the Terrestrial Manual was presented at the General Session by the Biological Standards Commission and adopted in May 2011. Part of the ongoing work of the Biological Standards Commission is to revise the section on rabies vaccine quality from the same manual, to make the most up-to-date expertise available to Member Countries. The working programme also foresees standardisation programmes for reagents, to facilitate the harmonisation of diagnostic testing, and work on scientifically acceptable criteria for validation of diagnostic tests in wild animal species.

As regards the OIE’s mandate to collect, analyse and disseminate animal health information worldwide, continuing developments over the last few years have provided improved support to Member Countries in fulfilling their reporting obligations or in retrieving the animal health information of other countries. WAHID allows differentiation of the disease occurrence codes and disease control measures applied in domestic or wild species (since 2009). The ongoing development of a new version of WAHID (WAHIS-2) and the development of WAHIS-Wild (a database dedicated to reported data on wildlife diseases in wildlife species) will offer a comprehensive list of known susceptible species so that the correct host animal can be reported (by family name, by scientific [Latin] name and by common name). Furthermore, a differentiation can be made between the occurrence of rabies virus and other lyssavirus species (e.g. European bat lyssavirus).

Improving transparency in notification through regular training of OIE delegates and their national OIE Focal Points, combined with enhancing the transfer of expertise, leadership and technology to all regions in need of global collaboration, are crucial for the OIE to achieve its goals of improving veterinary governance and, in consequence, encouraging better compliance with OIE international standards. Laboratory-based surveillance, combined with active health education and increasing public awareness, and the strategic utilisation of potent, inexpensive rabies vaccines in animals, are the highest priorities in preventing human deaths and are complementary, basic requirements for effective rabies prevention and control. In accordance with these requirements, the OIE has launched an initiative to establish the first OIE regional rabies vaccine bank, which will provide quality vaccine to countries in need located in the Southeast Asia region.
Last, but not least, since 2007 OIE Member Countries have had the opportunity to ask for an independent assessment of their Veterinary Services to verify whether they meet the quality requirements outlined in the *Terrestrial Code*. Member Countries may equally request that the OIE assist in the progressive improvement of the quality of the services they provide, using the evaluation of Performance of Veterinary Services (PVS) Tool. By the end of August 2011, 104 PVS evaluation missions by OIE-trained experts had been completed (out of 116 requests). The entire PVS Pathway (7) has proven to be one of the main levers for providing practical help to strengthen Veterinary Services, as it promotes sound governance and highlights any structural and procedural arrangements that may be needed, benefiting all disease control programmes.

**Conclusions/Recommendations**

Further progress in rabies control at the global level will depend upon the increased involvement of Veterinary Services and their partners. The capacity of Veterinary Services and other supporting institutions, both at the national and local level, needs to be strengthened. Rabies control should be considered to be for the good of the international community. For dog-mediated rabies, both national and regional awareness campaigns and institutional changes must be implemented. The findings of pilot OIE One Health PVS missions may further assist in the future, by determining the advances required for Veterinary Services to effectively collaborate with other sectors in the fight against zoonoses, including rabies.

Through its capacity-building programmes, global and regional conferences, and its network of Reference Laboratories and Collaborating Centres, the OIE supports Veterinary Services with policy advice, strategy design and technical assistance, for the diagnosis, control and eradication of rabies. The OIE and its partners will continue to develop more detailed guidelines on rabies control, with a focus on the institutional and legal frameworks for Veterinary Services (e.g. through the PVS pathway), and taking advantage of experience gained through several successful regional programmes.

**References**

Rabies control: other relevant international standards and policies

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Summary

Rabies has been increasingly documented in wildlife populations, presenting a serious risk to the management and conservation of affected animals. The rabies virus has been documented in over 120 mammal species. Several international treaties created to protect natural resources in general, and threatened, endangered and migratory species in particular, may affect rabies management approaches. These same international regulations may present impediments for rabies control programmes by limiting rabies intervention options, potentially presenting a greater opportunity for the spread of the virus in wildlife populations.

Keywords


Introduction

Rabies control remains a global concern for public health. While most human cases are transmitted by domestic animals, complete control of rabies requires comprehensive management in all affected species, wherever possible, and effective barriers to cross-species transmission in other situations. This reflects the burden of the rabies virus in humans, domestic animals and wildlife. In addition to representing a serious danger to humans and a significant disease for domestic animals, rabies has emerged as a major threat to the survival of certain wildlife species, broadening its relevance to include public health, animal welfare and the conservation of biodiversity.

Emerging infectious diseases in wildlife have been identified as a major threat to biodiversity, with rabies being a prominent example (7). With at least 130 mammalian species documented as susceptible to rabies virus infection, rabies clearly extends beyond humans and domestic animals. Of these susceptible species, the majority (>110) would meet the OIE definition of wild animals (Olival et al., unpublished data). The broad transmissibility of rabies across species, coupled with the dynamic nature of the disease in terms of the variety of virus strains and differing rates of prevalence and severity of impact among regions and species, make its control a persistent challenge. Additionally, there is no ‘one size fits all’ approach to the control of rabies in wildlife (1), with control strategies dependent on factors such as financial resources, wildlife management capacity and infrastructure, population dynamics, and the level of rabies risk and potential impact.
The lack of standardised control strategies for rabies is especially challenging in the context of wildlife management, given that several endangered species are affected by rabies. Cleaveland et al. eloquently state the resulting risk to wildlife, explaining that ‘…because few tools are available to control infections of wildlife, measures to control diseases associated with wildlife have often resulted in harm to wildlife…’ (2). With the increasing concern over the endangerment of wildlife populations, the importance of efforts to reduce harm and disease risk to wildlife must be established as a central tenet of control programmes. Additionally, the appropriate resources must be allocated to rabies control, as many wildlife managers are not prepared or equipped for responding to disease outbreaks (11).

As a global problem that compromises the health and survival of endangered species, the effective control of rabies relies on comprehensive multinational efforts. Thus, rabies must also be considered in the context of international standards that affect the control and protection of wildlife species and groups. Among these are the World Organisation for Animal Health’s (OIE) standards, which directly address rabies control through their classification of rabies as a reportable disease and their emphasis on rabies surveillance, diagnostics, and prevention. The others include the Convention on Biodiversity, the Convention on Migratory Species, the Convention on International Trade in Endangered Species of Wild Fauna and Flora, the Ramsar Convention, the International Union for Conservation of Nature (IUCN), the Red List of Threatened Species and the Convention on Conservation of European Wildlife and Natural Habitats.

**International standards affecting the control of rabies**

The Convention on Biodiversity (CBD) is a broad treaty of species protection, calling for ‘…the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilisation of genetic resources’. Recognised officially in 1993, the CBD now includes 193 Member Countries, 168 of which are signatories of the Treaty. It falls under the umbrella of the United Nations Environmental Programme (UNEP). While its clauses do not set specific regulations for rabies, its articles present implications for rabies control in wildlife. Of these, Articles 14 and 19 directly pose constraints for the control of wildlife diseases such as rabies (3).

Article 14 surrounds ‘Impact assessment and minimizing adverse impacts’, and calls for an environmental impact assessment for proposed projects with probable negative impacts on biodiversity and multinational discussions of activities that are likely to result in effects on biodiversity extending beyond national borders; as well as international agreements and cooperation for emergency responses to biodiversity threats. For example, assessments of the potential of the adverse impacts of interventions such as culling or fencing are stipulated by this article. The promotion of forward thinking with regards to intervention provides benefits to disease control. For example, an up-front assessment of rabies control programmes can inform wildlife and public health agencies about the costs and benefits to species. Rabies-control modelling studies can be used to guide population management strategies (7). A comprehensive and balanced assessment can help produce a pro-active understanding of the programme and its risks and benefits, potentially leading to the avoidance of ineffective or detrimental control strategies.

Article 14’s latter clause, regarding emergency response efforts, is particularly important for species with transnational ranges, as disease control strategies may vary markedly by country (15), hindering comprehensive and coordinated control. Additionally, given the potential for rapid rabies outbreaks in endangered wildlife species, and the mortality associated with such outbreaks, timely interventions are important.
Article 19 addresses the ‘Handling of biotechnology and distribution of its benefits’, urging parties to prevent adverse impacts on biodiversity from the use of biotechnology and modified living organisms. Vaccination must be considered in this context, as vaccination against rabies is a commonly used control strategy (1). Vaccination may pose some threats to animal welfare, as capture through trapping and vaccination itself may involve harm to target and non-target species, and has been ineffective in preventing mortality from rabies in some cases (11, 12). Thus, the benefits of vaccination to target species should be assessed to inform such interventions (11). Rabies oral vaccination, using baits for some wild carnivore species, has been broadly, safely and effectively used, though this approach has not been as effective for other species.

The Convention on Migratory Species of Wild Animals (CMS), or the Bonn Convention, was signed in 1979 and has 116 signatories. The CMS, which; ‘…aims to conserve terrestrial, aquatic and avian migratory species throughout their range…’, also falls under UNEP. However, unlike the CBD, it extends protection to specific species through its two appendices. Appendix I calls for the strict protection of migratory species which are threatened with extinction through a substantial part of their range, while Appendix II includes migratory species that need, or would significantly benefit from, international co-operation. The CMS includes two species in which rabies cases have been documented: *Acinonyx jubatus* (cheetah) (Appendix I) and *Lycaon pictus* (African wild dog) (Appendix II) (Table I).

<table>
<thead>
<tr>
<th>International treaty</th>
<th>Number of susceptible species listed</th>
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<td>Convention on Migratory Species of Wild Animals (CMS) or Bonn Convention (1979) (Appendix I and II)</td>
<td>2</td>
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<tr>
<td>International Union for Conservation of Nature (IUCN) Red List of Threatened Species (‘endangered’, ‘vulnerable’ and ‘near threatened’)</td>
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The Agreement on the Conservation of Populations of European Bats, or EUROBATS, was established under the CMS. EUROBATS extends protective measures to specific bat species. Thirty-three of 63 European, North African and Middle Eastern countries that are within the range of a bat species listed by EUROBATS are signatories to the Agreement, which seeks to protect bats; ‘…through legislation, education, conservation measures and international co-operation’. Currently, 52 bat species are listed as protected under the Agreement. EUROBATS holds potential implications for a large segment of rabies-affected species, as 73 bat species have been documented as susceptible to rabies (Olival et al., unpublished data). Although it was officially established in 1994, the impact of this Agreement is in its formative stage, with current efforts focusing on bat population research that will inform appropriate protective measures. It provides a forum for information-sharing and collaboration, as well as bat surveillance and research. This can help identify threats to bat species, and allow signatories to respond to potential disease threats in bats, such as rabies. EUROBATS may also benefit bat species heavily affected by rabies through formally listing them as protected species, as necessary.

The Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) addresses the protection of species through limitations on the trade of listed species. The Convention seeks to: ‘…ensure that international trade in specimens of wild animals and plants does not threaten their survival’. Entered into force in 1975, CITES has 175 countries in its membership. This Convention is specific in its trade quotas of listed species, setting export restrictions by country.
Species are listed across three appendices, with varying degrees of endangerment concern. Appendix I includes those that are most endangered; trade is allowed for scientific research only. Appendix II represents species with the potential for an extinction threat if populations are not closely controlled. Appendix III serves as a classification for special requests from trade regulators for species needing multinational cooperation (16). Eleven rabies-susceptible species are listed in the CITES appendices (Table I).

The setting and amendments of species export quotas allow for the consideration of many factors, including disease threats such as rabies. Permits are granted in limited quantities according to strict criteria. Listings of species provide an international basis for national laws against the export and import of CITES species without permits. Protected species without the appropriate CITES permits can be directly confiscated by CITES officials and national partners, discouraging their illegal trade. Thus, CITES can directly reduce the strain of exploitation on protected species, at least in the legal market, to prevent added population vulnerability for rabies-susceptible species resulting from their trade value.

However, CITES can also complicate the process of rabies diagnosis and control. Biological samples, such as blood or tissues, used for diagnostic testing are subjected to the same CITES requirements as the species from which they were obtained. Since applying for and obtaining CITES import and export permits can take a significant amount of time, there is the potential for a long delay when attempting to diagnose rabies in listed species from countries that do not have a national diagnostic capacity. Effective control of rabies is dependent on rapid diagnoses and rapid control responses. Delays of months or years while waiting for permits to transfer samples to a laboratory willing and able to perform the appropriate testing can result in the further spread of rabies, and an increased risk for wildlife, domestic animals and people.

The transmission of infectious diseases such as rabies can be increased through movement (9). Thus, the CMS and CITES have important implications for rabies control. In some cases, control strategies may consider limiting the movement of populations of rabies-affected species (9). This may directly contrast with the recommendations made by the CMS in protecting the natural range of migratory species. CITES, however, can reduce the movement of rabies host species through trade restrictions (although the illegal trade still represents a vulnerable area for disease spread).

The Convention on Wetlands, or the Ramsar Convention, aims for: ‘...the conservation and wise use of all wetlands... ...as a contribution towards achieving sustainable development’. Classification of ‘Wetlands of International Importance’, of which nearly 2,000 are listed, are backed by an ecological assessment that provides the basis for their inclusion. Containing species of importance is a factor in the assessment of the sites. For example, Sri Lanka’s Kumana Wetland Cluster includes threatened fauna such as *Elephas maximus* (Asian elephant) and *Panthera pardus* (leopard), both of which are rabies-susceptible species. By decreasing anthropological pressures on wetlands, rabies-susceptible species may have a greater chance of survival. The wise use of wetlands that Ramsar calls for should also consider the risk of disease transmission. For example, anthropogenic land use changes, such as the urbanisation of surrounding wildlife areas, may increase the risk of emerging disease infection and may introduce species that pose a disease threat (i.e. rabies) to wetland wildlife, domestic species and humans (17).

The IUCN Red List of Threatened Species also provides an international resource for the protection of species whose survival is of concern, through relative risk assessments of extinction. The Red List scientifically assesses the status of plant and animal species in taxonomic groups (not just threatened species), issuing a ranking ranging from ‘least concern’ to ‘extinct’. The assessments, which are updated at least every four years, incorporate ecological information, including threats such as rabies.
Of the mammalian species with documented cases of rabies, ten are classified as ‘near-threatened’, ‘vulnerable’ or ‘endangered’ (Table I). While these species do not necessarily receive formal protection through the Red List, member parties to IUCN include governments and organisations. Thus, the Red List provides ecological risk information for policy-makers, potentially influencing species protection. Assessments include a section on ‘Conservation actions’, providing transparency on the state of conservation efforts for the species.

The Convention on Conservation of European Wildlife and Natural Habitats, or the Bern Convention, provides a regional framework for species protection. The Convention strives to: ‘…conserve wild flora and fauna and their natural habitats and to promote European co-operation in that field’. Established in 1979, its signatories include European nations as well as some countries in Africa. Appendices II and III of this Convention list protected fauna species, with those in Appendix II receiving special protection, and those in Appendix III receiving extended protection which is open to regulated exploitation. The Bern Convention directly presents rabies control as a warranted example of an exception to its clauses in Article 9 of its associated Explanatory Report, as, ‘…there might be emergency cases where exceptions would have to be made without all conditions having been fulfilled (e.g. the abatement of rabies)’ (6). The mention of rabies in this context provides acknowledgement that rabies control may not always be synonymous with overall wildlife protection efforts.

**Benefits and constraints of frameworks in the context of rabies control**

There are both benefits and challenges presented by the above frameworks when viewed in the context of rabies control. The following cases of *Lycaon pictus* (African wild dog), *Canis simensis* (Ethiopian wolf) and *Acinonyx jubatus* (cheetah) demonstrate variations of application and effectiveness.

*Lycaon pictus* (African wild dog) is an example of a species susceptible to rabies which is receiving attention from international protective frameworks. Ranked by the IUCN Red List as ‘endangered’, the population has faced several causes of widespread decline, such as loss of habitat, deliberate and accidental killing, and infectious diseases including rabies (10, 13). Rabies outbreaks have extirpated entire packs, with die-offs recorded despite vaccination attempts (1, 10). Following the extinction of a protected Kenyan population due to rabies, *Lycaon pictus* was added to the CMS Appendix II as a species ‘designated for cooperative actions during 2009–2011’ (5). This was warranted under CMS as *Lycaon pictus* is a species with large home ranges (~70% of the population potentially crosses international boundaries), that functions in low-density populations, and has a highly social pack dynamic that increases the risk of rapid disease transmission (5, 10, 13). Thus, biodiversity frameworks provide an opportunity to directly extend protective regulations in response to the impact of rabies.

*Canis simensis* (Ethiopian wolf/simien fox) represents another example of a species affected by rabies. While it is ranked as ‘endangered’ by the IUCN’s Red List, the species is not listed in the other treaties discussed, as it is not directly relevant to the treaties that specify protected species. The species has a confined alpine range in Ethiopia and lives in highly fragmented areas. It has suffered high mortality and significant decline due to rabies, and now has a population estimated at fewer than 500 adult individuals (11, 14). In the case of *Canis simensis* and other endangered species that are not listed as migratory, wetland or CITES species, broad frameworks such as the CBD are especially important for nations to use when considering endangerment risks specific to their own country.
International standards and regulatory framework

International treaties can also indirectly help to protect species susceptible to rabies and minimise the downstream effects of outbreaks. As rabies can cause wide-scale population losses, it can directly affect trophic structure in wild animal populations which may impact upon the survival of endangered species. The case of the cheetah (*Acinonyx jubatus*) in Namibia in 1982 presents a prime example of this relationship. Although *Acinonyx jubatus* is susceptible to rabies, its population was not directly compromised by the rabies outbreak in wildlife, which caused widespread loss of game animals in the country. However, the outbreak’s wild animal losses caused a surge in cheetah predation on livestock. This led to mass killings of cheetahs by ranchers trying to protect their livelihoods, as there was no system in place to compensate ranchers for their livestock losses. An amendment to cheetah export quotas in Namibia was accepted into CITES, which permitted the export of cheetah hunting trophies in order to provide financing that would encourage farmers to tolerate cheetahs on their land by providing them with an alternative financial compensation for their livestock losses, and discouraging a ‘kill at any cost’ management approach. The quotas also included provisions for live cheetah export to promote successful preservation of cheetahs in captivity (4, 16). Thus, CITES presents an international regulation that considers risks to wildlife in a national, ecological and economic context.

**General benefits for rabies control in the context of international frameworks**

The international standards discussed within this paper provide frameworks for the direct protection of biodiversity, particular species, or the ecological areas that support them. In theory, they can help to reduce overall pressures on species, which could otherwise result from activities such as habitat destruction, wide-scale trade/economic exploitation, and ill-informed environmental interventions.

While only the Bern Convention directly indicates an exception to its terms for interventions intended to abate rabies, all discussed standards have implications for rabies control. They reduce the risk of species eradication, and the effective implementation of their clauses relies on the involvement of wildlife authorities and evidence-based interventions. Their influence creates an international forum for acknowledging the importance of the practice of species protection.

Additionally, the frameworks promote an ecosystem perspective in wildlife management, promoting multidisciplinary collaboration and sound approaches to control risks to species, especially risks posed by anthropogenic effects. Convention parties are accountable for their countries’ actions, discouraging inactivity and encouraging proper implementation of systems to protect wildlife and wild areas. Conventions also facilitate knowledge-sharing among parties, potentially arming resource-limited nations with the ability to promote species protection. For example, Article 19 of the CBD directly encourages the equitable sharing of biotechnology results and benefits with other Convention parties, particularly developing nations.

Disease control and ecosystem health rely on long-term, multi-species research, paired with cross-discipline collaboration from the public health, veterinary, and wildlife fields (2). International frameworks represent a forum for such collaborative and long-term consideration of risks and benefits to species and ecosystems. Treaty amendments must go through proposal and approval processes that can take several years and allow for expert and Member consideration in order to receive official integration into the treaties’ texts. Species lists have a defined set of ranking criteria, ensuring consistency and objectivity among assessments and listing decisions. Thus, frameworks can help promote systematic approaches to species protection that could potentially apply to the control of population threats such as rabies.
General challenges for rabies control in the context of international frameworks

What is generally beneficial for overall biodiversity protection – for example, avoiding culling native species – may be appropriate for rabies control. However, in the protection of biodiversity, prioritising the protection of individual species becomes complicated. Tiered appendices and rankings, such as the listings provided by CITES, CMS and IUCN, can help to guide species protection efforts. However, the potential for the spread of rabies to other species, potentially those with a greater threat of endangerment, makes the control of rabies challenging and introduces uncertainty around species conservation. The frameworks could provide additional value by better addressing wildlife disease threats related to the treaties’ purposes and by clarifying the best courses of action. For example, frameworks related to the movement of species should suggest appropriate actions to control diseases with wide transmission, such as rabies in migratory species.

The frameworks vary in their ease of implementation and interpretation. Broad treaties, such as the CBD, leave room for interpretation of their articles, while others, such as CITES, provide more direct actions for implementation (although implementation may be limited by personnel or financial resources). The absence of a species from the listing may falsely create the sense that the species does not warrant protection, potentially limiting the attention and resources received for promoting its well-being. Thus, parties to the conventions should use such treaties as a starting point for the protection of species, but not as the only or complete guide to conservation and wildlife health efforts. Clearly, governments must also consider their particular needs and efforts to protect species in a national ecological context.

International standards as a whole are limited in their protective effects. The treaties are only as good as the infrastructure that is developed to encourage and enforce them. Countries must commit to following the treaties’ content, but their success depends on the implementation of strong national policies, with the application of resources and enforcement to support the frameworks. Resource-limited nations may encounter challenges in implementing international agreements. For example, CITES enforcement and reporting varies markedly between countries, limiting its overall effectiveness in regulating trade of endangered species (8, 18). For wildlife populations with transnational boundary ranges, actions delivered in one country may do little good for the overall population if other countries are not similarly acting to protect the species. This is also a concern for disease control programmes, as nations may use varying control strategies.

Interaction of treaties also poses a challenge. Signatories and clauses are not uniform across the treaties, limiting the potential synergies of the frameworks’ goals and actions. The Liaison Group of the Biodiversity-related Conventions, which includes the CBD, CITES, CMS and Ramsar, met for the first time in 2004 to help address such concerns by providing a mechanism for sharing information and promoting collaboration and benefits among the treaties.

The slow pace of treaty amendments serves as a potential constraint to the control of a population threat such as rabies. Threats to species are typically addressed under international frameworks in a reactive, rather than pro-active, manner. Rabies represents a dynamic disease – strains vary and evolve – and transmission is dependent on numerous population and ecological factors. Rabies may represent an immediate threat of extinction (2). Thus, the inability to respond rapidly to a rabies outbreak could have negative conservation implications.
Conclusion

Success in rabies control cannot be limited to elimination of human cases. We must seek to control rabies throughout the domain of all adversely affected species, while recognising that eradication of rabies in all susceptible species around the world is not feasible. Thus, the definition of success in rabies control might be better described as a point in time when most cases of rabies are found in only a small number of wild species, which are minimally affected and pose little risk to humans and other animals. To progress towards this goal, international frameworks should facilitate species sample movement to allow for disease testing, promoting the early identification of rabies in wildlife. Vaccine development and widespread global use must be a cornerstone of international health and conservation standards in order to move towards healthier populations, largely free from rabies. Additionally, international treaties, policies and regulations must address the challenges of disease control and prevention as they relate to the purposes of the standards.

Recommendations

Current regulations often prevent the rapid collection and international movement of diagnostic samples from wildlife for testing. Governments and international bodies are urged to modify regulations to facilitate timely diagnostic sample collection and shipment.

The control of rabies in wildlife requires the rapid and open sharing of genetic material from both wildlife hosts and virus strains. Governments and international bodies are urged to ensure that regulations and treaties allow for this rapid international collaboration to improve disease control.

For most endangered and threatened species, the availability of safe and effective vaccines could contribute to reducing the disease in the species at risk and lessening spillover to other species, including humans. There is a need to continue to develop new vaccines and test current vaccines for safety and efficacy in wildlife before disease outbreaks occur.

Governments are urged to have pre-approved rabies prevention and control strategies for wildlife species, rather than to wait for rabies outbreaks to occur. These approved procedures should include appropriate vaccine choice and delivery options, as well as the collection and transport of diagnostic specimens.

Public health and wildlife health authorities need to review rabies prevention and control strategies to ensure compliance with relevant international treaties and regulations aimed at protecting wildlife. Working with counterparts in government agencies delegated to represent these treaties and regulations could open useful dialogues and collaborations to assist in preventing and controlling rabies.

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References


Local governments, municipalities and dog rabies control

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Summary

Over the past 44 years KwaZulu–Natal (KZN), a province on the eastern seaboard of South Africa, has been battling endemic canine rabies. The implementation of a system of solid regulations, good surveillance and sound veterinary infrastructure has achieved some success in controlling the disease, but elimination has eluded the efforts of the programme. This paper aims to elucidate the factors, events and circumstances that have played a role in the successes and disappointments in controlling rabies in KZN. Most recently, with international support and sponsorship (Bill & Melinda Gates Foundation and World Health Organization), the KZN Rabies Project has taken significant steps towards the ultimate goal of eliminating rabies. We assessed the role of local governments and municipalities, communication strategies and programme sustainability in the context of the current project and the history of rabies control in the province. As would be expected, we demonstrated that it was essential to determine the true extent of herd immunity in the KZN dog population, which is in turn determined by the methods and approaches used in mass vaccination campaigns. We found that failures resulted from institutional pressure on the rabies control programme, including political pressures, financial constraints, poor management and shifting priorities (outbreaks of other diseases of economic importance, etc.). Successes, on the other hand, were largely dependent on the establishment of a core team of capable and motivated individuals. It appears that, in a setting such as KZN, the sourcing of committed and passionate individuals at the local level has been a key component in the creation of a platform from which there is a realistic chance of eliminating rabies, regardless of the considerable constraints and challenges prevalent in the developing world.

Keywords


Introduction

Today rabies is recognised as a neglected disease (www.who.int/neglected_diseases/zoonoses/), and this indictment defines the lack of progress in many countries around the world, with regards to canine rabies control. The classification ‘neglected’ implies that the solutions to the disease are well known but that those responsible have failed to react appropriately. This being true of rabies, valid and important questions need to be considered. This paper considers what aspects are being neglected and the levels at which such neglect primarily occurs.
Today, the most important tools required for rabies control are readily available (www.rabiesblueprint.com). There is no real need for new 'magic bullets' to deal with the disease, and this is particularly true in KwaZulu–Natal (KZN). We know from experience that the disease can be eliminated by well-organised campaigns that utilise any of the commercial high-quality parenteral vaccines available for vaccination of dogs, the sole reservoir of rabies in KZN. Although new biologicals such as oral rabies vaccines and immunocontraceptives for use in dogs may well be useful adjuncts to assist in control and elimination, failure to control rabies commonly arises not from a lack of tools or new biologicals but from failures in application and strategy.

Yet laws governing the control of the disease in many rabies-endemic countries, including South Africa, are good. Standard operating procedures for the use of vaccines and implementation programmes are good and even globally available (e.g. the Blueprint for Rabies Prevention and Control). It is therefore reasonable to question the global failure of canine rabies control. From our experience with rabies control efforts in KZN, we conclude that governmental commitment to the implementation of rabies control acts and regulations is a fundamental element in the failure or success of such ventures. In this regard, the performance of officials at the local government level is also crucial.

**Results**

**Forty four years of efforts to control rabies in KwaZulu–Natal**

A year-by-year analysis of the prevalence of rabies in KZN over the past 44 years immediately reveals periods of high prevalence interspersed with periods of lower prevalence (peaks and troughs). Closer examination allows for an alignment of these varied prevalences with circumstances such as good or poor management, political interference or support, and other disease priorities (outbreaks) (1). The aforementioned factors all influence the effectiveness of governmental rabies control programmes and ultimately determine the levels of population immunity and disease prevalence. Interferences, such as those mentioned, are characteristic of the developing world, and the importance of committed, persistent individuals dedicated to overcoming multiple obstacles and working towards any measure of success in rabies control programmes can be appreciated.

**National Acts and Regulations**

Local control measures are determined by National Acts of Parliament and their regulations (2). In South Africa these are robust and have stood the test of time, with rabies control currently falling under the Animal diseases Act 35 of 1984 (control disease) and the Health Act 63 of 1977 (notifiable disease).

The Animal Disease Act comprehensively deals with all aspects of rabies control: from diagnostics, control measures and vaccine regulation to the provision of resources, nationally and provincially. At the provincial level this is then managed by the provincial services, both health and veterinary, and naturally cascades down to local level.

However, the process of dissemination of authority leads to important variations in practice, as different provinces have different infrastructures and therefore different abilities to implement such regulations (4). Each province is a unique entity and faces different challenges in implementing these laws. This process is often further diluted at the municipal level, as a new set of circumstances dictate the ability of districts to achieve service delivery. One of the aspects that affect these differences is local infrastructure: the strength of the municipal management, personalities, corruption, etc. Thus, by the time laws reach ground level there is great variation in the quality of implementation, and the control of diseases such as rabies is perceived as being of relatively low importance in comparison with greater challenges such as combating human immunodeficiency virus or tuberculosis or the provision of basic services such as water and electricity.
Local governments

In KZN, it is local politics, infrastructure, leadership, economics, the ecology of areas and the attitudes of officials that dictate the level of interpretation and implementation of laws and regulations. In dealing with this in terms of more effective rabies control, the starting point would be to recognise the uniqueness of each country, and the individual provinces and municipalities therein. There are almost an infinite number of circumstances that drive local communities to deal with matters such as rabies differently, and a strategy, although in essence relying on the same fundamentals, should be planned according to the characteristics of the local governments and communities. Ultimately these characteristics and behaviours can be seen as drivers for the persistence of rabies in the corresponding dog population.

Existing and new biologicals

The existence and availability of potent vaccines, together with multiple examples of the successful use of vaccination to achieve herd immunity and eliminate canine rabies, should be reminders of past advances and breakthroughs in the field of rabies control. Importantly, although the mechanisms and biologicals to achieve elimination of canine rabies are proven and available, it should be realised that there are no shortcuts in achieving this goal. New biologicals may offer some theoretical advantages, with respect to ease of vaccination, vaccination efficacy or population control, and we argue that such improvements should be pursued. However, there is no excuse for not achieving effective control of canine rabies with existing biologicals and methods. In this respect, it is important to realise that there is no quick fix and that rabies control requires sustained commitment to appropriate and comprehensive vaccination strategies and equally thorough surveillance.

Successes in KwaZulu-Natal

The variety of activities within the KZN BMGF (Bill & Melinda Gates Foundation) World Health Organization (WHO)-administered rabies elimination programme are summarised in Figure 1. Over time, KZN has been particularly successful in several aspects of rabies control:

- improving post-exposure prophylaxis (PEP): Dr John Godlonton was instrumental in improving the quality of PEP delivery across KZN, and today PEP (with locally produced human rabies immune globulin) is free for the treatment of any cases of potential exposure to the rabies virus
- human rabies surveillance: Dr Godlonton was instrumental in creating awareness and material for the recognition and management of rabies in humans
- diagnostics, surveillance and awareness of rabies in the dog reservoir and other animals: Mr George Bishop and Butch Bosch established a rabies diagnostics service in KZN, which now services three provinces. Mr Bishop and Dr Paul Kloeck were also responsible for a system of rabies awareness, including an excellent video, that greatly improved the understanding of rabies throughout the province
- rabies control in dogs: Dr Max Bachmann first introduced the concept of mobile vaccination campaigns in KZN. This system was gradually improved in subsequent years, and current standard operating procedures are shared globally (www.rabiesblueprint.com).

In support for our general premise, as stated above, it is evident that specific individuals made the above achievements possible, often in the face of opposition and apparent lack of support/funding. However, as such individuals retire, move or pass on, gaps are left and interest wanes. From this perspective, succession and a continuity of leadership must be a primary goal of any plan. In KZN, more recent supportive research has focused on various aspects of rabies epidemiology (Fig. 1) (6), and included a comprehensive study of KZN dog ecology. The provincial government also supports a $2.7 million primary healthcare plan for the KZN dog population. Significantly, over the
last four years, the programme has achieved a 62% drop in animal cases – representing successive year-by-year decreases in rabies cases and the most sustained period of continual decline of rabies cases in the history of KZN. The KZN rabies control programme also celebrated a 12-month human rabies-free period in June 2011, marking the first human rabies-free year in 20 years.

**Fig. 1**

*KwaZulu–Natal rabies eradication programme (Republic of South Africa)*

**What makes the KwaZulu–Natal example interesting or relevant?**

KwaZulu–Natal represents a dedicated canine rabies control programme in an African region. Despite the challenges inherent to all developing regions of the world, this programme is driven by a committed and passionate team and has, as a result, attracted some attention from the outside world. As a consequence, with international support, the programme is expanding its area of influence and creating a momentum that is influencing provinces and countries around it. From this perspective, and given the quest to control rabies in dogs and prevent human rabies globally (in particular in Africa and Asia), the KZN example may well offer a promising formula.

With respect to disease control, national and local governmental frameworks are essential (3), as it is within these that legal control functions are possible. However, with respect to any specific disease, such policies may not be executed/applied because of other priorities and lack of infrastructure. In the case of KZN, one pathway to elevate the priority given to rabies was through a rabies action group. This group brought together different interested and enthusiastic stakeholders and was a major contributor to the rabies agenda at a municipal and local level. In our experience, success at these levels can in turn influence strategies at higher levels and ultimately impact on national strategies.

The firm establishment of a single point of reference for all matters related to rabies and rabies control has greatly contributed to the success of the KZN programme over the past 4 years. Previously, control measures were left up to individual districts, resulting in variations in quality of control and little coordination. The establishment of a single rabies control unit has allowed for standardisation, focused effort and cooperation, and channelled support to the programme (7).
Conclusions and recommendations

‘Organization doesn’t really accomplish anything, plans don’t accomplish anything either, theories of management don’t much matter. Endeavours succeed or fail because of the people involved. Only by attracting the best people will you accomplish great deeds’. (Colin Powell, former United States Secretary of State).

In the global effort to find solutions to rabies problems in developing countries, KZN is one example of how such a programme can develop and be implemented. In the experience of this programme, the role of specific individuals, with appropriate succession where required, is the primary determinant of success or failure. Quite rightly, international support often follows only after rigorous evaluation of the merits of such support and requires at least a proven and existing commitment that could effectively benefit from recognition and additional support.

The WHO-administered BMGF rabies programme in KZN demonstrates this concept (6). This support, although a relatively small supplement to the total project cost, was most significant by virtue of in-kind aspects of recognition and facilitation of global collaboration and support from the global WHO collaborating centres and the World Organisation for Animal Health (OIE) Reference Laboratories, among others.

Acknowledgements

We would like to thank WHO and BMGF for invaluable support. We also thank the Alliance for Rabies Control, the Partners for Rabies Prevention and the global World Organisation for Animal Health reference laboratories for their leading roles, interest and collaborative support. The authors thank the KZN veterinary staff and vaccinators, who deal with difficult conditions every day, for their tireless efforts.

References

Rabies control and animal welfare

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Summary

The welfare of animals in countries in which rabies is endemic is frequently ignored. This is largely because of the gravity of the human health problem, and this, combined with ignorance of the best methods for controlling the disease and hence protecting human health, can, and often does, result in extreme animal suffering. The disease itself causes great suffering in animals, including farm animals, wildlife, cats and dogs, as it does in humans. The World Organisation for Animal Health (OIE) guidelines on stray control lay down practical and humane ways of controlling rabies in the stray and owned dog population. One of the problems that needs to be overcome is the attitude of the authorities – veterinary services, national and local competent authorities and police – towards stray animals, both cats and dogs. It is important that these authorities are persuaded of the need for a holistic approach to dog control rather than proposing the slaughter of dogs as the only solution. A vaccination programme for animals, particularly dogs, is a vitally important control measure, and, although it may appear expensive at the time, it will eventually prove to be economically beneficial. This paper will demonstrate how changing the socioeconomic and public health attitude towards rabies control and, in some instances eradication, can be achieved. Controlling and eradicating rabies is not impossible and, if achieved, will have enormous economic as well as human and animal health benefits.

Keywords


Introduction

Why is animal welfare important?

The lives of animals and humans are inextricably linked, so the question ‘Why is animal welfare important?’ could be expanded to ‘Why is animal welfare important to human welfare?’ However, this implies that animal welfare is not important in its own right. We could ponder the philosophical, moral and ethical arguments and how they pertain to the value of animals, but the truth is, when we talk about the welfare of animals and the need for animal welfare, nobody ever claims that what is really needed is more animal suffering and cruelty and poorer welfare for animals. Animal welfare is, of course, important for a broad range of reasons, not least of which is recognising the intrinsic value of the animals themselves, but before we examine these wider aspects we perhaps need to ask another question: ‘What is animal welfare?’
Animal welfare could be described as the desire to prevent unnecessary animal suffering. That is, while not categorically opposing the use of animals, wanting to ensure that they have a good quality of life and a humane death. The ‘five freedoms’ (5) provide a framework for the scientific assessment of animal welfare:

- freedom from hunger and thirst
- freedom from discomfort
- freedom from pain, injury or disease
- freedom to express normal behaviour
- freedom from fear and distress.

While defining animal welfare measures in this way, we can also add additional components to measure levels of suffering by considering the prevalence, duration and severity of that suffering.

**Animal welfare and the dog population**

There are an estimated 770 million dogs around the world (8), of which approximately 75% are thought to be stray or roaming. If we consider their welfare, we can begin to see the broader implications for these dog populations.

Do these dogs have freedom from hunger and thirst? In many cases stray or roaming dogs are likely to suffer from malnutrition, starvation or thirst. Do these dogs have freedom from discomfort? There can be a lack of adequate or appropriate shelter, especially during extremes of weather. Do these dogs have freedom from pain, injury and disease? There can be a high prevalence of skin diseases and related infections in stray and roaming dogs, a high risk of other diseases and conditions such as distemper, rabies, parvovirus infection, and tumours, a high incidence of injuries sustained from road traffic accidents, and worldwide there is a high stray puppy mortality rate (12). Do these dogs have freedom from fear and distress? There can often be competition for available resources with other dogs and a regular threat of aggression from both dogs and humans. It could be argued that these dogs probably do have the freedom to express their normal behaviour, but this is significantly compromised by the suffering experienced in the failure to meet the other four freedoms.

Dogs suffer greatly in attempts to decrease or control their populations. In instances in which inhumane culling is used for population control, dogs are the victims of poisoning, shooting, gassing, electrocution, bludgeoning and drowning. Where shelters or pounds are used, street dogs are often placed in massively overcrowded and inappropriate facilities that cause them stress and increase susceptibility to disease. There are often insufficient resources for the dogs and no hope of being rehomed. Additionally, there are serious welfare issues associated with the methods of catching, handling, restraint and transport of these dogs. Even in cases where this is done as part of a ‘humane’ control programme, there can still be considerable suffering if those carrying out the work do not have the correct knowledge, expertise, training and equipment.

All of this is important, but a balance clearly needs to be struck between the welfare of dogs and the welfare of the human population. We know that dogs are the vector for 99% of human rabies deaths globally (15) and that more than 3 billion people are living in canine rabies-endemic countries in Asia (14). Dog bites are a significant public health problem. For example, there are as many as 17 million dog bite cases in India each year (16). We know that dogs are often seen as a cause of road traffic accidents (10) and that dogs are often perceived as a ‘nuisance’. They bark, foul public areas, can cause property damage, and contribute to the loss of livestock and wildlife through both predation (4) and diseases such as rabies (3).
However, we also know that dogs can enrich human lives through companionship and security.

The priority is to safeguard human welfare, but this does not have to be done at the expense of dogs. The problem is essentially that of limited resources. The argument against incorporating animal welfare often assumes that it will prove to be a hindrance, a burden or an added cost. When human welfare is low animal welfare is seen as a lower priority; it would, in theory, be good to integrate the two but not at the expense of human welfare. In fact, the adoption of good animal welfare principles can directly benefit human health (6). Animal welfare does not have to be a peripheral issue or a hindrance – it can be central to a project’s success.

Stray and roaming dogs exist; they are a fact of life and a reservoir for rabies (16). The choices we have are to kill them, impound them or vaccinate them. We know that the mass removal of dogs can impede vaccination coverage and increase the risk of disease dispersal (1). It also fails to address the source of the roaming dog population and will therefore need to be repeated indefinitely. Additionally, the sudden reduction in dog numbers through mass removal leaves greater resources for surviving dogs, leading to their increased reproductive success and survival rates, thereby rapidly rebuilding the dog population (16). We also know that a stable and safe (i.e. vaccinated) dog population is the best defence against rabies (1).

These facts are supported by the following statements:

- ‘There is no evidence that removal of dogs alone has ever had a significant impact on dog population densities or the spread of rabies’ (TRS 931, World Health Organization [WHO], 2005).
- ‘Mass canine vaccination campaigns have been the most effective measure for controlling canine rabies’ (WHO, 2005).

We also know that by vaccinating 70% or more of the total dog population we can eliminate rabies in humans (16). This has been demonstrated both theoretically and by empirical observation and holds true irrespective of other dog population management or supplementary control measures (7). However, additional dog population management interventions can provide additional benefits: a decrease in dog population turnover (7); a decrease in the numbers of ‘high-risk’ young dogs and breeding behaviours (11); a decrease in the numbers of unowned dogs (17); a decrease in the number of dog bites (2); and an increase in the perceived ‘value’ of dogs.

**Vaccination programmes**

If we are to undertake a successful mass vaccination programme there are critical factors that must be utmost in our planning. The mass vaccination should be achieved quickly and systematically, proceed in a consistent and uniform manner and be based on a survey of the total dog population, not simply on the number of registered dogs. All vaccinated dogs should be identified with a temporary mark of some kind and there should be an assessment of vaccination coverage based on post-campaign surveys, not simply on the number of vaccines used. The programme should be achieved in full cooperation with the community, sensitising it and the wider public to the issue and ensuring that there is confidence in the campaign by demonstrating humane handling and good standards and practices. The programme should also encourage owners to bring and restrain their own dogs and promote the essential concept of responsible companion animal ownership.

The World Society for the Protection of Animals (WSPA) has supported many canine rabies control projects with partner organisations around the world.
In Colombo, Sri Lanka, WSPA has been working with its local partner organisation, the Blue Paw Trust, since 2007. From 1990 to 2006, rabies was endemic within Colombo. A non-systematic vaccination strategy had been implemented by the Colombo Municipal Council (CMC), but each year the city authorities also undertook the mass culling of between 2,000 and 4,000 dogs.

Over that period one-third of the city’s dogs disappeared from the streets but rabies did not. Then in 2006 CMC decreed that dogs could no longer be killed. In 2007, WSPA and the Blue Paw Trust, with the cooperation of CMC, began a coordinated mass dog vaccination and public education programme across the city. By 2008 dog rabies cases had halved, and they continued to fall year on year as the vaccination programme continued. By the end of 2010, an estimated 89% of the dog population (15,000 dogs) had been systematically vaccinated, and by the end of 2011 the number of canine rabies cases across the city had decreased by approximately 92%. There had also been a significant reduction in the number of dog bite cases (WSPA, unpublished data).

Prior to 2008, Bali, Indonesia, was rabies free and had an estimated dog population of 400,000. Rabies is thought to have been introduced via a fisherman’s dog arriving from one of the neighbouring islands. The first reported cases of canine rabies were confined to the southern peninsula, where the fisherman’s dog had arrived. In November 2008 the first human rabies case occurred. Initial attempts at vaccination and restricting the movement of dogs failed to stop rabies spreading from the primary outbreak site to the rest of the island. In early 2009 culling was introduced in an attempt to control the rabies outbreak (13). In December 2009, WSPA and its local partner organisation, the Bali Animal Welfare Association (BAWA), ran a pilot mass vaccination project in Gianyar, one of Bali’s nine regencies. The aim of the project was to demonstrate that mass vaccination is possible and effective and to provide the necessary training to replicate this model across the entire island. In May 2010 the pilot project in Gianyar was completed, by which time approximately 45,000 dogs (> 70% of the dog population) had been vaccinated. Evidence showed that the mass vaccination had been more effective than culling, even when culling was paired with vaccination efforts, and, additionally, there had also been a significant reduction in the number of dog bite cases (WSPA, unpublished data). In September 2010, the mass culling of dogs across the island officially ceased. With the cooperation and support of the Balinese authorities, WSPA and BAWA, along with the support of other international partners, implemented an island-wide vaccination campaign, and by March 2011 the first phase of this vaccination programme had been completed. Approximately 210,000 dogs (70% of the island’s remaining dog population) had been vaccinated. A comparison of the 4-month period from December 2009 to March 2010 with that from December 2010 to March 2011 showed a 48% decrease in the number of human rabies cases and a 45% decrease in the number of dog rabies cases (WSPA, unpublished data).

In May 2011, WSPA commissioned the Royal Veterinary College and the University of Glasgow (United Kingdom) to undertake a full economic and cost–benefit analysis of both the Colombo and the Bali projects. The results of this research are due to be published in 2012. The resulting data will give a comprehensive and comparative breakdown of all the costs and benefits associated with both projects. There are several elements to be examined within the analysis. These include the direct costs the vaccination programme will accrue from its planning, preparation, and implementation and the activity costs, which would include data collection for monitoring purposes, data analysis and the interpretation and communication of the results. Additionally, there are the costs of any future post-eradication activities such as surveillance and border inspections. The benefits can be divided into two categories: the financial benefits to be gained by avoiding certain costs and the non-financial benefits that can be gained by avoiding certain costs. The financial benefits include the gains to be made by avoiding the costs associated with human post-exposure prophylaxis, the cost of epidemiological investigation of any human deaths and the negative impact a rabies epidemic might have on tourism. Among the non-financial benefits are the avoidance of dog bites in humans (thus avoiding the pain and distress suffered by bitten individual as well as the emotional impact of the illness or death of that
individual on their family and the community), the avoidance of the inhumane culling of dogs (thus preventing the distress suffered by humans when their dogs are killed or when they witness dogs being killed on the street), and avoidance of the slow painful death from rabies of infected dogs or the euthanasia of rabid dogs.

**Comprehensive dog population management**

Ultimately, it could be argued that any costs or savings arising from a rabies eradication programme are largely immaterial without public support. It is interventions that also directly address human behaviour that will have the greatest, most sustainable, impact on dog welfare, dog populations and the effectiveness of any rabies eradication campaign. Incorporating responsible ownership is integral to the long-term solution and there are essential elements to this. We need to understand that the majority of dogs perceived as 'stray' have or have had some form of ownership (9). We need to identify owners, potential owners and community carers and help them take responsibility for the dogs. Registration should reward, not discourage, responsible ownership; if there are heavy fines of people may kill or hide their dogs, which would reduce vaccination coverage. However, all dogs, regardless of registration status, should be vaccinated. Both for dog welfare and for rabies control, we want dogs to be responsibly owned.

The eventual goal is that every dog has someone to take responsibility for its welfare and for the risk that it poses to others. Ultimately, we should simply recognise the value of dogs in human society and the crucial role that dog welfare plays in rabies control.

**References**


Awareness and communication programmes for eliminating rabies at the animal source

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Summary

The best way to prevent human deaths from rabies is to eliminate rabies in dogs. Effective and sustainable rabies control programmes require community engagement, public health partnerships and committed intersectoral support in carrying out mass vaccination, localised education and targeted communications. Health communication is the key to raising awareness about rabies among those most at risk and is the backbone of the World Rabies Day Campaign. Creating a communications strategy helps convert scientific data into purposeful information and is a cross-cutting component of future aspirations for successfully and sustainably eliminating rabies at the animal source.

Keywords


Introduction

The Global Alliance for Rabies Control believes that it is only through partnerships and working together that we can reduce the burden of rabies in humans and animals (4). The most efficient and effective way of preventing rabies in humans is to eliminate the source of infection, and, as over 99% of all human deaths occur after exposure to an infected dog, this means conducting mass vaccination programmes against rabies for dogs living in canine rabies-endemic regions.

Rabies is one of the oldest diseases known to mankind. The means by which to prevent it have been available for decades, yet people continue to die every day. The main reason why humans still die of this preventable disease is that they do not receive post-exposure prophylaxis (PEP), as recommended by the World Health Organization (WHO), after an exposure (9). This may occur for several reasons, including a lack of awareness about the need to seek medical care; a lack of knowledge about proper wound care and how to administer PEP; insufficient money to buy vaccines; and a lack of access to rabies biologicals (7).

Rabies prevention and control strategies must involve an intersectoral approach if they are going to be successful (5). Technical expertise from international organisations such as WHO, the World Organisation for Animal health (OIE) and the Food and Agriculture Organization (FAO) can provide a platform for designing rabies prevention programmes that should include, at a minimum, multidisciplinary teams of specialists from the fields of human and veterinary public health, education and communications, legal and paralegal systems, and finance and administration. Volunteer and non-governmental organisation contributions can help to expand the number of people involved in the
day-to-day activities of rabies prevention programmes, making them far more effective and cost-beneficial. Finally, community-based support for rabies prevention programmes is critical, not only for effective implementation but also for assuring sustainability at the local level.

Education is often overlooked when it comes to implementation of rabies prevention programmes, and yet it is a powerful tool for improving awareness across the general public. Without the knowledge of what to do after being exposed, a bite victim will not seek PEP and may not understand that wound care is a critical first step to preventing rabies. Therefore, there is an urgent need to educate communities living at risk, especially the children who are most often affected and least informed. Education also involves building advocacy and communications programmes that will inform and engage communities to vaccinate dogs, treat animals with respect and to be responsible companion or community dog owners.

**Targeting communications**

It is often the case that data do not equate to information, and, for public health interventions to be effective, information must be appropriately communicated to diverse audiences, most of which consist of individuals outside the scientific community (3). To achieve this, scientific data must be transformed and translated into understandable information that is both made available to and actionable by the targeted end-recipient(s). By working closely with the scientific community, health communicators can often help to convert complex data into more apparent, useful information. Health communication is a hybrid discipline and requires understanding of behavioural science, health education/promotion, journalism, business, clinical professions, political science and information technology. Similar to most public health interventions, successful communication is based first and foremost on scientific knowledge. Programmes are initiated once sufficient evidence exists on the value of a behaviour change. The planning framework for developing an effective communications plan can be divided into eight steps (Table I). By evaluating the community to be accessed and working with them to design prevention messages that are culturally sensitive and scientifically correct, behaviour modification can be achieved that will ultimately result in saving human lives.

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<tr>
<th>Step</th>
<th>Planning</th>
<th>Question to be answered</th>
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<td>1</td>
<td>Assess the science</td>
<td>What is the scientific evidence?</td>
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<td>2</td>
<td>Define the purpose (inform or persuade)</td>
<td>Why is communication necessary?</td>
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<td><strong>Inform</strong></td>
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<td>- Increase knowledge</td>
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<td>- Facilitate informed decision-making</td>
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<td><strong>Persuade</strong></td>
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<td>- Individuals: change attitude or behaviour or learn a new skill</td>
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<td>- Governments: change or maintain programme, policy or law. Change or maintain resources</td>
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<td>3</td>
<td>Identify the audience(s) and understand the characteristics</td>
<td>Who is the audience?</td>
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<td>4</td>
<td>Develop and test message concepts</td>
<td>What is the message?</td>
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<td>5</td>
<td>Chose media and channels</td>
<td>How and where should the messages be delivered?</td>
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<td>6</td>
<td>Determine timing</td>
<td>When should the message be disseminated?</td>
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<td>7</td>
<td>Implement the plan</td>
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<td>8</td>
<td>Evaluation</td>
<td>Did the audience receive the information and was it effective?</td>
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*Table I*

*Eight steps in the development of an effective communications programme (3)*
Opportunities

Over the past five years, communications focused on reducing the number of human rabies deaths by aiming to eliminate the disease in dogs have dramatically increased. New opportunities that have evolved through the increased understanding of health communications include: World Rabies Day, public–private partnerships such as Partners for Rabies Prevention (PRP); and the expanded use of electronic communication. All three programmes have opened opportunities to improve support for eliminating rabies at the source of infection.

World Rabies Day (WRD), launched in 2007, is observed annually on 28 September, the anniversary of the death of Louis Pasteur, in honour of his contribution in developing the first effective human rabies vaccine (10). WRD is the single largest health communications campaign focused on rabies. The campaign began as a single day of action and has evolved into a year-round initiative to mobilise communities to get involved in local efforts to control rabies and to urge governments to support national rabies prevention programmes. Since its initiation, WRD has sent educational messages to over 150 million people in over 150 countries across the world and is now included on the United Nations website of annual health days (8). In 2010, a survey was conducted in four languages, and, of the 213 participants who responded, 96% stated that rabies education is saving lives, 89% indicated that WRD is making a difference in their communities and 95% indicated that they would host a WRD event the next year (2). New and rejuvenated dog vaccination programmes have enabled over six million animals to be vaccinated across the world as part of the rabies prevention initiatives conducted around WRD.

Public–private partnerships help to provide the backbone for developing intersectoral rabies prevention and control strategies. PRP is an excellent example of a successful public–private partnership. Since its inception in 2008, it has brought together stakeholders from across the world to find workable solutions to help reduce the number of human rabies deaths by focusing on increasing access to information related to rabies prevention strategies, improving interaction between major stakeholders in the field of public health, and developing and working on common goals to reduce the global burden of rabies. Key initiatives of PRP have included the development of a road map for global rabies prevention and control that focuses on increasing global awareness; the support of mass dog vaccination programmes and improved use of human rabies biologicals; and the launch of a free online resource, the Blueprint for Rabies Prevention and Control (1), an easy-to-use accessible gateway to all the information required to prevent human cases of canine rabies. The Blueprint provides links to international resources, as well as many examples from various countries explaining how successful programmes can be developed to halt the spread or reintroduction of canine rabies, and serves as a valuable guidance document for any country interested in diminishing the burden of human rabies by targeting elimination of the disease at the source of infection.

Finally, the global burden reassessment study represents the first stage of a communications plan (Table I) and aims to gather the information needed to reignite communications about the need for rabies control at an international level.

Global accessibility to the Internet has increased dramatically over the last decade, and the utilisation of electronic communications techniques has revolutionised how educational messages can be accessed across the world. Resources relevant to rabies control, previously impossible for many people to access, are increasingly being made available on many organisations' websites. The Global Alliance for Rabies Control has built an international global network of public health experts non-governmental organisations, veterinarians, medical practitioners, laypeople and others working in the field of rabies prevention and has facilitated the sharing of their expertise and resources for the benefit of local communities living at daily risk of contracting rabies. For example, the Global Alliance for Rabies Control has established a repository of educational material focused on both animal and
Role of various stakeholders in rabies control in the animal reservoir

human rabies prevention. These materials are freely accessible, available in many different languages, and continue to serve as valuable educational tools for those that need them (6).

Novel methods for bringing rabies workers together electronically and in real time to discuss expertise and share experiences in local rabies control practices from different countries continue to be provided by the Global Alliance for Rabies Control. For example, in 2010 and 2011, the Alliance hosted two annual rabies ‘webinars’, or web-based seminars, on WRD. An estimated 665,000 listeners joining from approximately 500 locations across 83 countries logged in to participate in these webinars, thus providing access to the latest rabies information from global and in-country experts without incurring a huge investment in travel and associated conference costs.

Examples of communication in action

The Global Alliance for Rabies Control has supported many community-based education programmes throughout the world. Two successful intersectoral programmes with large communications components warrant mentioning here. The first project was located in the province of Bohol in the Philippines, an island of about 1.3 million inhabitants. This community-based project was a collaborative programme conducted in conjunction with the provincial government. The sustainable project focused on eliminating the ever-rising number of human rabies cases by focusing on registration and mass vaccination of dogs. The success of this project was hugely dependent on effective communication to engage the communities, enlist volunteer participation and increase awareness and enforcement of existing rabies laws and the registration of dogs. One hundred per cent of the small fee charged for dog registration is rolled back into the programme and is helping to sustain the financial cost of the effort. Additionally, another major contribution to maintain sustainability was secured by incorporating rabies educational messages and responsible companion animal ownership into the curriculum of all elementary schools on the island. This successful programme has not only eliminated rabies in humans and dogs but has established an enhanced surveillance system to identify any new rabies cases that may be reintroduced.

A second example of a successful intersectoral rabies prevention programme occurred in three villages outside Bangalore, India, and was conducted in collaboration with the Rabies in India Foundation and the Karuna Animal Welfare organisation of Bangalore. The programme focused on vaccinating dogs, educating children, improving access to human rabies vaccines, and, specifically, empowering village women to be the source of information for dog bite victims. This programme has built bridges between veterinarians, physicians, teachers, animal welfare experts and private industry, and, through effective communication, has engaged local citizens to collaborate in their approach to reduce the number of human rabies deaths in their communities.

Conclusions

In conclusion, it is clear that prevention of human rabies is possible. In order to create successful and sustainable programmes it is recommended that strategies be implemented that include support from multiple sectors of a community. Without a doubt, eliminating rabies at the main source of infection, i.e., the dog populations of Asia and Africa, will ultimately provide the best solution to reduce the number of human deaths across the world. However, focusing solely on initiating mass rabies vaccination programmes for dogs without involving other sectors of public health is unlikely to establish sustainable rabies control programmes. It is recommended that consideration be given to additional strategies that complement dog vaccination programmes when establishing national rabies control programmes. For example, improving awareness and education by investigating what would be the most appropriate and effective communication strategies for each target population, ensuring that rabies prevention laws are well established and enforced, and, finally, engaging and involving
local communities in national programmes is essential. Public–private partnerships can provide opportunities to pool resources and expertise and should not be overlooked in the planning stages of programme development. There are many tools in place to prevent rabies including excellent animal and human rabies vaccines, new diagnostic tests, free educational material and increased opportunities for training on effectively communicating rabies prevention information locally. However, to finally eliminate rabies at the main source of infection to humans, it is recommended that additional research be conducted to develop new methods to humanely control the ever-expanding dog population and to expand access to diagnostic tests and surveillance techniques. Finally, it is imperative to develop and support methods to improve sustainability in current and future rabies prevention and control programmes.

**References**


The economics of dog rabies control and the potential for combining it with other interventions

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Summary

Rabies control in developing countries is often haphazardly organised as a result of poor communication between the human and animal health sectors. Ministries operate with a narrow focus: for example, the Ministry of Health is unwilling to assume responsibility for an intervention outside the public health sphere, and the Ministry of Agriculture and Livestock prioritises cattle over dogs and wildlife. Neither is willing to allocate scarce resources to address a disease that is not its priority. An economic analysis of rabies control provides a framework to examine the benefits and costs of intervention. Benefits in terms of saved resources and human and animal lives across all affected public and private sectors can then be compared with intervention costs, considering potential sharing across sectors. We present a cross-sector public and animal health economic approach to rabies control that is based on a dog–human transmission model linked with a cost-effectiveness analysis. It can be adapted to specific contexts and matched with the Blueprint for Rabies Prevention and Control (www.rabiesblueprint.com). Inadequate financial and personnel resources impact the delivery of human and animal health services in most developing countries. Large distances and poor road infrastructure represent further challenges, necessitating new methods to ensure comprehensive provision of health services. Joint animal and human health studies in pastoralist communities have shown that veterinarians engaged in livestock vaccination programmes achieve better coverage than human health personnel. Dog rabies vaccination could be connected to such activities. However, such approaches are deeply context dependent, requiring careful insight into community sociocultural and provider aspects.

Keywords


Economic considerations of dog rabies control

Rabies is a disease of the central nervous system to which all mammals are susceptible and that without treatment shows 100% mortality. Infected animals shed the virus in their saliva and transmit it mainly through bite wounds to the next host. In the larger part of Europe, rabies has been successfully eliminated or restricted to small wildlife reservoirs, such that the disease has for the most part vanished from public awareness in Western countries. But there are still millions of people in the lesser developed world that live with the day-to-day risk of infection from a rabid dog. Actions against
the infection in humans are limited to providing bitten persons with post-exposure prophylaxis (PEP). But the necessary vaccines are mostly not available and/or not affordable. Owing to the lack of means in poor countries to protect exposed persons adequately from disease onset, rabies is estimated to account for over 55,000 deaths per year worldwide (12). A survey in Tanzania found that many people consider rabies a larger threat than malaria, despite malaria having a higher prevalence (3). The faint prospect of recovery and the dramatic progress of the disease up until death thereby play an important role.

The tools to eliminate the disease are well known, and the magnitude of the problem on a global scale has been identified (www.rabiesblueprint.com [12]). What is often lacking are the financial and infrastructural means of establishing strategies for a sustainable abatement. To keep the costs of an intervention to a minimum and at the same time gain the maximum long-term benefit, it is essential to understand the respective epidemiological situation. The fact that the huge number of partly unattended domestic dogs is responsible for approximately 95% of all human rabies cases is without controversy (World Health Organization, 2010; www.who.int/rabies/en/). In N’Djaména, Chad, it has been reported that one rabid dog exposes on average 2.3 persons (8). The majority of bitten individuals are children, who are more likely to be bitten on the head or the trunk, locations with a very high risk of actually developing rabies (2).

The World Health Organization (WHO) estimates that, over a period of 15 years, dog vaccination combined with PEP for exposed patients is more cost-effective than PEP alone, where the virus still circulates in the dog population (1). The WHO also estimates that the threshold vaccination coverage for rabies eradication in a dog population empirically is about 70% (4). Such coverage can be obtained only if owners are willing to vaccinate their companion dogs (6). The adequate interval between vaccination campaigns, i.e. how fast the virus can again spread in the population after intervention, varies from region to region. Many factors such as host population dynamics, population density and possible reservoir and vector species influence the epidemiology of the disease (10, 11).

Often, the transmission rate of the rabies virus in a dog population is low (7), in which case the elimination of the disease is possible. There are already several examples of successful interventions by dog vaccination campaigns (10). To assure long-term benefits and the sustainability of measures taken against rabies in a certain area, it is essential to obtain the participation of the community and the local authorities in such interventions. Elevated public awareness of rabies in a community helps to increase the number of vaccinated dogs and supports the prevention of bites in humans. As the propagation of rabies is heavily dependent on the circulation of dogs, in addition to a vaccination campaign, a legislative approach is needed to identify and register dogs and encourage dog owners to take responsibility for their animals. Through these measures contact between dogs can be reduced and dogs without owners can easily be identified (see the Blueprint for Rabies Prevention and Control, www.rabiesblueprint.com).

Here we summarise our experience with rabies control and the preparation for rabies elimination in N’Djaména, the capital of Chad, within a partnership of the Laboratoire de Recherches Vétérinaires et Zootchnique de Farcha (LRVZ), the Centre de Support en Santé International du Tchad (CSSI/T) and the Swiss Tropical and Public Health Institute (Swiss TPH). Based on a household survey, the number of dogs was estimated to be approximately 23,000 with a dog–human ratio of 1:21 (13). Dogs in N’Djaména are mainly kept as watchdogs. The majority of the dogs are free roaming, and one-third of them have to find their food in the streets. An estimated 19% of the dogs have been vaccinated against rabies by private veterinarians. The immunofluorescent antibody test (IFAT; World Organisation for Animal Health-prescribed gold standard for rabies diagnosis) has been established in the LRVZ, the reference laboratory of Chad, since 2000 (8), and, in parallel, the new alternative method, the direct rapid immunohistochemical test (dRIT; Centers for Disease Control) using light
microscopy, has been successfully tested (5). These studies showed that dog rabies was endemic in
N’Djaména with a yearly incidence risk of 1.4 per 1,000 unvaccinated dogs.

In a pilot dog mass vaccination campaign, a high vaccination coverage of 64% to 87% was reached
when the vaccination was free to owners (9). This corresponds with standard requirements to prevent
rabies outbreaks specified by WHO, which have been confirmed by earlier studies (3, 4). Following a
similar pilot vaccination campaign with a charge to the owner of about € 3, we found a vaccination
coverage of 24%, which was insufficient to interrupt dog rabies transmission. Assessing the
willingness of owners to pay for vaccination, we estimated that, to achieve a 70% vaccination
coverage, one dose of vaccine should cost at the most € 0.60 (Fig. 1) (6). As dog owners in
developing countries can hardly afford to have their dog vaccinated against rabies, we argue that
freedom from dog rabies should be declared as a goal for global public good.

![Fig. 1](image)

**Fig. 1**

*Average probability of having a dog vaccinated against rabies by charge for vaccination: observed (undulating line) versus owner-stated values (straight line) (6)*

A dog–human rabies transmission model has been developed, analogous to a livestock–human
brucellosis transmission model (14). It is a tool to assess the comparative cost-effectiveness of
different rabies control strategies. Based on the present model, rabies control interventions can be
simulated. Currently, based on model outputs we hypothesise that the transmission of rabies could be
interrupted by a single parenteral mass vaccination campaign of all 23,000 dogs in N’Djaména. Such a
successful vaccination campaign would be possible because the propagation of the virus proceeds at
a low and stable endemic level, with a reproduction ratio of nearly 1. According to the model, rabies
could be eliminated in the city area over a period of about 6 years. Beyond that period it appears that it
would be more cost-effective to combat rabies through mass vaccinations of the dog population than
through the administration of rabies PEP to affected individuals alone (Fig. 2) (17). Currently, a dog
rabies elimination campaign is being prepared in N’Djaména, aiming for the elimination of dog rabies
by two consecutive dog mass vaccinations in 2012 and 2013. A general framework for the
comparative costs of dog rabies control can be derived from Figure 2. The respective costs of human
PEP and dog vaccination may differ by context. In Figure 3, we present a generalised framework
depicting the area where the comparative cost of dog rabies vaccination becomes lower than that of
PEP alone (dotted line). Similar cross-sector dog–human studies are needed to validate this
proposed framework.
Saving human lives is the main benefit of rabies control. However, the notion of benefits must then be expanded to put a value on the lives of companion animals and wildlife conservation, both of which are part of the ‘integrity’ of the ecosystem. Hence, we move into an ecosystem health approach to rabies control (www.ecohealth.net). The human–animal relationship is strongly determined by culture and religion. These influence animal populations and, therefore, indirectly rabies transmission, illustrating the complex interplay between natural science and humanities and supporting systematic dynamic approaches to health in social–ecological systems (18).

**Fig. 2**

**Comparative costs of human post-exposure prophylaxis (black line) and dog mass vaccination campaign (grey line)**

Diamonds are break even points at different discounting rates (3%, 5% and 10%) (17). Reproduced with permission of Proceedings of the National Academy of Sciences of the United States of America (PNAS).

**Fig. 3**

**Generalised framework for the comparative costs of post-exposure prophylaxis (PEP) (solid lines) and dog mass vaccination (dashed lines)**

The dotted line encompasses the area where the cost of dog mass vaccination is lower than that for post-exposure prophylaxis.

**Combining dog rabies control programmes with other interventions**

Inadequate financial and personnel resources impact the delivery of human and animal health services in most developing countries. Large distances and poor road infrastructure represent further challenges, necessitating new methods of ensuring the comprehensive provision of health services.
Joint animal and human health studies in pastoralist communities have shown that veterinarians engaged in livestock vaccination programmes achieve better coverage than human health personnel. Trials done in Chad over several years showed that combining human and animal vaccination services is feasible and conserves financial resources when compared with single-sector campaigns (15). However, such approaches are deeply context dependent, requiring careful insight into community sociocultural and provider aspects. Participatory stakeholder approaches, which involve local communities, authorities and technical experts, allow for identification of local priorities for disease control in animals and humans (16). Tailoring interventions to the needs of communities optimises the use of scarce resources and may lead to unexpected collaboration across sectors of public services. Using this type of approach, rabies control would be integrated into an overall animal and human health approach, rather than being addressed using a single sector vertical operation. Rabies vaccination of dogs could be incorporated in joint human and animal vaccination campaigns for remote rural populations in Africa, or be part of brucellosis mass vaccination efforts in Central Asia and Mongolia. Consequently, remote populations could be reached more efficiently, with a significant reduction in intervention costs, hopefully to affordable levels. Additional contextually adapted, community-based studies are needed to substantiate the technical and economic evidence for inclusion of rabies control in other animal and public health interventions, possibly as an extension of the Blueprint for Rabies Prevention and Control (www.rabiesblueprint.com). Remote rural communities could also contribute more effectively to wildlife rabies prevention and control.

Recommendations

– Dog rabies elimination should be concentrated on dog mass vaccination if political will and adequate funding exists.

– Dog mass vaccination could be combined with other interventions, even those in human health.

– Freedom from dog rabies should be declared as a global public good.

References


New approaches in dog rabies control programmes


Assuring the quality and sustainability of a rabies dog vaccination programme: vaccination, rabies surveillance and post-vaccination monitoring

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Summary

The annual number of human rabies cases is estimated at more than 55,000, more than 99.9% of which occur in Africa and Asia, in areas where rabies is mediated by dogs. One technique that has shown to be effective in achieving long-term prevention of human rabies is the coordinated mass vaccination of dogs. A stepwise mass dog vaccination programme, based on various international guidelines, could be organised as follows. The first phase is to establish adequate interlinked rabies surveillance systems and networks for both animals and humans. Surveillance is of utmost importance to determine rabies incidence, to identify areas for vaccination, and to assess the success of vaccination campaigns. The second phase is to study local dog populations to estimate the proportion of ownerless and owned dogs that are impossible to vaccinate. This will influence the choice of the vaccination strategy (parenteral or parenteral in combination with oral when the proportion of inaccessible dogs is over 30%). As soon as continuous adequate long-term financial funding of a rabies control project is guaranteed, based on available surveillance data, a National Committee for Rabies Control, comprising all stakeholders, should decide the area to be vaccinated, the vaccine to be used, additional measures to be taken (complementary oral vaccination of dogs) and the monitoring system to be implemented to assess the impact of vaccination campaigns.

Keywords


Introduction

Canine rabies is responsible for over 55,000 human deaths each year (14), with more than 99.9% of cases reported in Asia and Africa. Each human death is entirely preventable as efficient vaccines and biologicals are available. As for foxes, any conventional rabies control measures aiming to control canine rabies by reducing the dog population have been shown to be inefficient and even counterproductive. Canine vaccination programmes appear to be the most effective tool to control rabies in those countries where dogs are the reservoir and vector of the disease (8). The ultimate objective of a rabies vaccination strategy is to build sufficient herd immunity in the reservoir species,
i.e. dogs, to prevent transmission of the rabies virus and spillover infections to other animal species and humans. To be efficient, vaccination coverage should be 70% and be maintained in vaccinated areas for the whole duration of the programme (5). This level is often not achieved because rabies is neglected and because canine rabies control is not part of a national programme dedicated to rabies elimination. In areas where regular and long-term control efforts target dogs, thanks to strong commitment from national authorities, current mass vaccination programmes are successful and cost-effective, and elimination of canine rabies is achievable (8). Knowledge of the local dog population is a prerequisite for an efficient rabies control policy. It is also useful in the control of other dog-mediated diseases such as hydatidosis and leishmaniosis. Regular information campaigns about rabies and its control and strong media support increase awareness and contribute to the success of dog vaccination programmes and also to the sampling of animals required for rabies surveillance.

A number of international guidelines on canine rabies control are available. World Health Organization (WHO) consultations have been organised, and concrete recommendations and road maps are available for planning, implementing and evaluating strategies for rabies control in dog populations (15). The World Organisation for Animal Health (OIE) has recently published a guideline for stray dog population control (20). The global community of rabies experts, Partners for Rabies Prevention, has produced the Blueprint for Rabies Prevention and Control (www.rabiesblueprint.com), which provides concrete recommendations on various aspects of preventing human death and controlling rabies in dogs (9). In those areas where canine rabies is endemic, disparate groups of stakeholders and policy-makers in human and animal sectors meet on a regular basis: SEARG (Southern and Eastern African Rabies Group) consists of experts from 18 countries sharing data to define actions to control rabies; AfroREB (African Rabies Expert Bureau) is a similar group for French-speaking Western African countries that collects data on rabies burden and increases the awareness of rabies; and AREB (Asian Rabies Expert Bureau) gathers experts from nine Asian countries. Information on the practical aspects of rabies control and prevention is now available; there is a need to translate that information into action.

The reasons for the ineffectiveness of canine rabies control measures have been analysed and published (8) and suggestions for action plans and road maps for both human prevention and animal control have been reported (8). This report is intended to present, on the basis of the different experiences of the authors in African and Asian countries, the key elements required for effective and sustainable dog rabies control programmes based on mass parenteral vaccination. The use of oral vaccination against rabies for dogs will also be discussed.

**Main prerequisite for dog rabies control: an integrated approach (the ‘One Health concept’)**

In countries where canine rabies is endemic, there have been several successful experiences of a sustained rabies vaccination programme (7, 11). To be successful, rabies vaccination programmes cannot be undertaken as a unique approach. Institutional and political decisions involving both human and veterinary sectors are the key basis of an integrated approach for rabies control programmes: rabies should be a notifiable disease in both humans and animals. The legal basis is also of utmost importance as it ensures political commitment. National laws, as well as possibly regional and local legislation and decisions, should exist, both for human prevention and animal control. National and local authorities should work in close collaboration, as should the human and veterinary sectors.

A sustainable programme needs also to nominate a project coordinator dedicated to the management of a network of identified persons, each of whom has specific and complementary responsibilities to the project (Table I). A legal framework must also be in place, as well as an assurance of long-term budget allocation.
It is highly advisable to constitute a National Committee for Rabies Control including representatives of all sectors involved in the programme. This committee should be chaired by a person from the agricultural authority. It should gather members from the agricultural, health, education, environment and interior affairs authorities. Representatives of animal welfare organisations and associations and non-governmental organisations that are directly involved in the field, as well as private veterinarians, should also be part of this network. Regional and local authorities must also be represented. The objectives of this partnership network are to regularly share information on the rabies epidemiological situation, both in humans and in animals (particularly dogs), and to coordinate the different activities of the programme.

Table I

Main responsibilities at national, regional and local level in the different sectors involved in rabies prevention and control

<table>
<thead>
<tr>
<th>Veterinary authority</th>
<th>Human health authority</th>
<th>Education authority</th>
<th>Interior affairs authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propose and write a strategy</td>
<td>Propose and write a strategy</td>
<td>Provide information for schools: books, videos, films, posters, etc.</td>
<td>Organise refuse elimination (containers)</td>
</tr>
<tr>
<td>Calculate a budget</td>
<td>Calculate a budget</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organise dog population studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquire inactivated rabies vaccine for dogs</td>
<td>Acquire inactivated rabies vaccine for humans and immunoglobulins</td>
<td></td>
<td>Remove stray dogs, ABC programme</td>
</tr>
<tr>
<td>Organise, implement and monitor vaccination campaigns for dogs</td>
<td>Organise PEP to assess availability of vaccines and whether available all over the country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register and identify dogs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declare and report to ad hoc authorities all positive cases in animals</td>
<td>Declare and report to ad hoc authorities all positive cases in humans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organise surveillance of suspect animals and evaluation of the programme</td>
<td>Organise surveillance in humans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collaborate with local authorities, animal welfare NGOs, private veterinarians, etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promote responsible dog ownership</td>
<td>Education of general public</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NGO: non-governmental organisation
PEP: post-exposure prophylaxis

Defining a strategy for control

The annual budget dedicated to the global strategy and to each component of the programme, even approximate, should be known to all involved sectors before deciding which strategy to implement. The strategy of prevention and control should be readapted to this budget annually: it is more cost-effective to regularly vaccinate a small area to maintain satisfactory coverage among the dog population (and then a continuous decrease in the incidence of rabies in humans) than it is to vaccinate too large an area with a low coverage. As a first step, pilot projects in limited areas could be
conducted with the support of local and national authorities; this method is of great interest (17) to test the practical feasibility of the measure and its impact. Where they are successful, such initiatives encourage replication of the project on a larger scale.

The strategy for a dog vaccination programme is established after assessment of the rabies situation in different parts of the country. An estimate of the density and the classification of dogs is also required to give an idea of the proportion of dogs in the area that can be vaccinated by the parenteral route. These estimates need to be derived from both field studies and questionnaire-based surveys (15). Those questionnaires and field surveys also allow an assessment of the interest in oral vaccination as part of the campaign to improve vaccination coverage, if necessary.

As the programme is the responsibility of national stakeholders, the choice of areas to be vaccinated should be validated at the national level prior to its approval at local levels. The overall project includes the practical organisation of the vaccination campaigns, dog population management in certain areas, rabies surveillance and evaluation of the programme.

The vaccination protocol should provide details for the followings items: areas to be vaccinated; name and mobile telephone number of person with overall responsibility for activities, as well as those of other persons involved; precise method(s) of vaccination employed (central point or/and house-to-house parenteral vaccination); dog identification method, if any; injectable vaccine used (batch numbers quoted); means used for transport and storage of vaccines; materials used (syringes, needles); models of grids to complete; and the duration and frequency of vaccination campaigns (generally annual vaccination). Once established, the plan for each campaign should be transmitted to all participating organisations and people with sufficient notice before the start of the campaign to allow them to get organised.

Injectable vaccines containing at least 1 IU per dose, produced on cell culture following current guidelines, inactivated and possibly adjuvanted, must be used. Safety (control of the inactivation process) and stability during long storage in both liquid and lyophilised forms are important parameters in guaranteeing the quality of vaccines used. It should be noted that charging dog owners for rabies vaccination is known to increase the responsibility of owners for their dogs and the sustainability of the control programme; however, it may also discourage owners from bringing their animals to the central vaccination point. In this case, the questionnaire study may be helpful.

Besides vaccination at private veterinary clinics, which are poorly used in rural areas, mass vaccination campaigns may be organised at one or several central points in the cities. This strategy is considered the most cost-effective and it is particularly well adapted to dogs that are semi-restricted or fully restricted (6). Door-to-door vaccination is also commonly used for semi-restricted and aggressive dogs. This strategy requires a strong commitment on the part of owners and local authorities. It also requires careful organisation to record the houses visited, and several teams may be required to vaccinate at the same time to cover a large area. Prior to starting the vaccination campaign, it is highly advisable to have the support of local authorities and raise the awareness of the general public, including children, to convince them that it is in their interest to have their dog vaccinated. If there is sufficient budget, dogs could be vaccinated against other diseases or de-wormed, resulting in an improvement in its condition, and this ‘visible’ effect and may prompt people to bring their dogs for boosters in the future.

Low vaccination coverage can also be explained by the size of stray dog population, as well as inaccessible owned and ownerless dogs that cannot be vaccinated using injectable vaccines.
One of the aims of dog population studies is to evaluate the ‘ownerless’ and ‘not accessible to parenteral vaccination’ portions of the dog population; such dogs should be orally vaccinated to obtain a 70% vaccination coverage only if they represent 20% to 30% of the dog population. Since 1988, WHO has released several guidelines and recommendations encouraging the launch of pilot studies combining oral vaccination (using the wildlife-derived model) and parenteral vaccination. Oral vaccination trials using rabies vaccine contained in baits attractive to dogs have been undertaken for several years on different continents to test the feasibility of this method, which is, regrettably, still not used routinely over large areas as a complement to parenteral vaccination to control canine rabies (4). As for parenteral vaccination, the method of distribution of vaccine baits has to be adapted to local conditions. The wildlife-derived model consists of depositing baits in places where groups of dogs are found; however, as those vaccines are not 100% safe, unconsumed baits must be removed from the area. Another aim of pilot studies is to determine the attractiveness of the bait, as well as its efficacy for dogs, in local conditions.

Immunisation coverage, as well as rabies incidence, are improved if all teams work efficiently. To achieve this goal, teams involved in dog vaccination should be trained for this purpose. If an area is not correctly vaccinated, the incidence of rabies will increase in that area and neighbouring areas will be reinfected.

Considering the data available on the immune response of puppies to rabies and the fact that they are frequently in close contact with children and may be easily caught during vaccination campaigns (2), all puppies, whatever their age and the immune status of the bitch, should be vaccinated during mass parenteral vaccination campaigns. This greatly helps to increase the vaccination coverage of the dog population.

Dog population control programmes (20) should be a complement to dog vaccination campaigns, including mainly sanitary measures (such as dog removal or adoption programmes), particularly regarding waste management and reproduction control through animal birth control programmes (15). Immunocontraception is a promising tool specifically for controlling the reproduction of dogs in well-defined areas and periods of time (16).

**Rabies surveillance**

Data from rabies surveillance are a crucial step starting point for a campaign. The ultimate indicator of the efficacy of the control programme will also come from surveillance data: a decrease in the incidence of human and animal rabies in vaccinated areas. Rabies surveillance is therefore the basis for any follow-up on the efficiency of vaccination. It must be based only on laboratory investigations on dead or sick animals sampled from all parts of the country and throughout the year (not on dogs killed at random) using reference techniques to diagnose rabies (18). The OIE recommends only that an effective system be in place (19) but no specific sample size recommendations are given. Animals (owned or ownerless) suspected of having the disease are those to which humans might have been exposed (biting, scratching or licking on broken skin), animals showing clinical signs suggestive of rabies or abnormal behaviour, and also animals found dead.

A number of reports have already stressed the importance and objectives of a rabies surveillance network (12), the most important point being an effective partnership among all sectors involved in rabies (Fig. 1).
EXAMPLE OF RABIES SURVEILLANCE NETWORK

SUCH NETWORK MUST HAVE A LEGAL BASIS (LEGISLATION ARTICLE)

Evaluation of the programme

Laboratory investigations on animals collected in the field are undertaken for rabies diagnosis and, if possible, for typing of positive isolates for further epidemiological analysis. In areas where an injectable vaccine has been used for the first time during a mass vaccination campaign, a serosurvey of vaccinated dogs allows evaluation of the immunogenicity of the group (vaccine + vaccination strategy) in field conditions (13). This is particularly important when changing the strategy or when using locally produced inactivated vaccine to assess the ability of the vaccine to induce a protective immunological responses in dogs, if not already done.

The measure of rabies-neutralising antibodies in blood samples should be achieved in a defined number of dogs that are sampled on the day of vaccination and 30 days later. The peak of rabies-neutralising antibodies is generally reached between four and six weeks after the first antigenic stimulation. Thereafter, levels of antibodies decrease very rapidly, and may be under the 0.5 IU/ml threshold as early as some weeks after vaccination, irrespective of the quality of the vaccine (10). It is possible that a dog with a low level of antibodies (less than 0.5 IU/ml) after vaccination may still be protected if seroconversion was achieved before that time (3). A serosurvey performed too long after vaccination will underestimate the real protection conferred on the animal population and could lead to misinterpretation regarding the efficacy of the vaccine used or of the campaign organisation. Interpretation of the results should take into account the fact that rabies-neutralising antibodies produced after vaccination are similar to those produced after exposure to the virus, but it must also take account of the fact that the probability of seroconversion as a result of rabies infection in an apparently healthy dog is very low. Animal bite injury data obtained from hospitals could be of help in assessing the rabies burden following vaccination (1). The National Rabies Control Committee has...
responsibility for analysing the data from rabies surveillance and identifying possible gaps and opportunities for improving the programme. Decisions regarding extension or reduction of the programme or a change in vaccination areas should be taken on the basis of results obtained, particularly those on rabies incidence, bite injuries and vaccination coverage, and also taking into account available funding and human resources.

Conclusions

To be sustainable, rabies control programmes based on mass vaccination of dogs using injectable inactivated vaccines should be integrated into a multi-year campaign to eliminate rabies, including a human rabies component. It is necessary to obtain sufficient vaccination coverage to interrupt the transmission of the virus at the individual level and to maintain this vaccination protection until rabies elimination has been proven. To achieve this objective, governments should ensure uninterrupted long-term funding. Oral vaccination trials should be considered in those areas where rabies control using injectable vaccines has not been a success in order to increase vaccination coverage.

References


New approaches in dog rabies control programmes

Public and private funding sources for sustainable rabies control programmes

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Summary

Rabies control is often not among the disease priorities of public health and agriculture ministries, therefore effective comprehensive implementation has always been a challenge. Conversely, being a disease that crosses different sectors of society and diverse disciplines, intersectoral rabies control programmes benefit from human and animal health fund sources from different sectors at different levels of society. Many innovative approaches have been attempted to overcome constraints such as high operational cost, wide coverage areas, and labour intensity. A recent example of a successful, sustainable community-based integrated rabies control programme is the Bohol Rabies Project, implemented as a partnership between the provincial government of Bohol, in the Philippines, and the Global Alliance for Rabies Control. Funds were generated by the communities, all of which were reinvested to establish a self-sustaining funding stream.

Keywords


Introduction

Despite being an entirely preventable disease, rabies continues to kill at least 55,000 people every year, most of them children under the age of 15 years (2). Because rabies control is often not among the disease priorities of the public health or agriculture ministries, mobilisation of resources for effective comprehensive implementation has always been a challenge. On the other hand, being a disease that crosses different sectors of society and diverse disciplines, it has the advantage of being able to tap into the collective efforts of many stakeholders and multiple sources of funds and human resources.

Funds for disease control programmes have traditionally been sourced from local and national governments and international development aid. Actual implementation of intersectoral rabies control programmes often requires and depends on a regular budget allocation as mandated by law. Governments that are committed to implementing disease control programmes provide the institutional framework, legislation and policies, infrastructure and logistics, human resources and fund appropriation. International organisations and aid agencies offer funding and technical inputs, set guidelines and standards, and have monitoring and evaluation mechanisms.

There are numerous examples of public–private partnerships that contribute to public programme implementation, support research and promote policy development (3). A number of rabies control programmes in humans and animals have sourced funds from different sectors at different levels.
The range of sources could be from the grassroots to the corporate and civil society organisations. General support to local governments given by civil society organisations includes community mobilisation, volunteer services and some donations of materials. The business sector can give direct donations or embark on joint ventures. The academic community can conduct research and offer technical inputs, voluntary services and student manpower. The community contributes taxes, fees for services, donations and volunteer manpower.

Field implementers and partner communities may face constraints such as high operational costs, wide regions of coverage and labour intensity. Many innovative approaches have been attempted to overcome these problems. There are numerous lessons of good practice learnt from experience. A recent example of a successful, sustainable community-based integrated rabies control programme is the Bohol Rabies Project, implemented as a partnership between the provincial government of Bohol, in the Philippines, and the Global Alliance for Rabies Control (GARC). The project brought together educators, physicians, veterinarians, government officials, community leaders and the general public, and aligned them for a coordinated effort (2).

The estimated operational cost was US$498,000 over four years. Cost-sharing by different stakeholders was achieved through mobilisation of financial and human resources. The Philippine government provided 60% of the programme funds required. GARC contributed 33% through collaborative funds raised from socio-civic partners. Some funding came from the World Health Organization (WHO) Country Office and local non-governmental organisations (NGOs). Community volunteers were organised to augment the human resource requirement. Manpower grew from 124 paid government staff to 15,021 people (including thousands of village-based volunteers and teachers).

This programme produced a significant shift in rabies control, from government-dependent implementation to a community-led movement. Funds were generated by the communities through collection of dog registration fees, all of which were reinvested to establish a self-sustaining funding stream. A small fee is charged for dog registration, to help fund the ongoing programme costs and subsidise human post-exposure vaccines. The programme steadily enforced mandatory dog registration and vaccination. Making this a legal requirement secured long-term sustainability. The involvement of community volunteers was key to the project’s success but also meant that the overall programme budget was less than $0.40 per person over four years.

The Philippines is among the top 10 countries in terms of deaths from rabies. In 2007, when GARC began its rabies control project, Bohol was ranked fourth in terms of rabies deaths in the Philippines, averaging 10 deaths per year. To date, only one suspect human case has been reported since October 2008. People’s understanding of the disease has improved, and they now seek and are provided with proper medical assistance rather than turning to traditional healers. An unexpected benefit of the project has been a significant reduction in the number of road accidents caused by stray dogs. It has allowed the growing tourism industry to flourish, contributing to the local economy. The impact of controlling rabies in Bohol has gone beyond saving lives. Sustainable and meaningful field operation was realised when acceptance and ownership of the programme at the community level was achieved. Attaining the goal of rabies control and eventual freedom from disease became a shared concern.

**Whole-of-society stakeholder involvement**

In any disease control programme, wide stakeholder involvement is critical. It is important to bring together key stakeholders from business and the public sector to discuss health security and the importance of establishing public–private partnerships (1). Contributions from private organisations, including businesses, the academic community and civil society, can be both tangible and intangible.
Tangible contributions are generally in the form of donations in kind or money. Intangibles are such things as voluntary contributions, which should be maximised. The intention of this paper is to depict a tried and tested system of public–private partnership that resulted in province-wide rabies elimination. GARC has served as a conduit for business sectors, international NGOs, academic institutions and civil society organisations to extend their financial and technical assistance to government. GARC is also serving to promote standardised approaches to rabies control and elimination and promote the start-up of public–private partnerships that will ensure sustained intervention. Such a technical and administrative conduit is essential and beneficial to all stakeholders, providing the credibility and quality assurance that is directly rooted in day-to-day field operations.

International and local NGOs such as GARC provide support in project management, fundraising, pooling of resources, technical inputs and guidance, and often act as an intermediary between donors and government (Fig. 1).

Fig. 1

Innovative funding and resource mobilisation

Challenges of public–private partnerships

The continued assurance of private-sourced funds depends on the effort made to acquire these funds; thus, fund-sourcing must be a full-time effort that requires a wide range of committed stakeholders. In the case of the ongoing GARC-supported rabies programmes, the credibility that has been established through these programmes facilitates fund-sourcing. Thus, organisations such as GARC must project technical and managerial competence amid political uncertainties. Experience in the field has shown that there may be disincentives to the provision of external assistance, including an uncertain political environment, a lack of political support and inadequate counterpart funding (4).
Conclusions

The key to the success of the GARC public–private partnership model is the centrality of GARC itself as a key partner architect of the rabies control and elimination programme framework and strategic plan. Its role includes ensuring evidence-based and informed programme planning, institutionalised organisation, policies and implementation mechanisms, the setting in place of clear performance indicators, and uninterrupted resource inputs. The key steps in project integration within the local system are the identification of key persons or technical and political champions, clear and functional feedback channels among partners (e.g. internal and external monitoring), encouraging government empowerment and programme ownership and stakeholders’ participation, and formally defining the roles and responsibilities of stakeholders through memoranda of understanding. Increased public awareness and understanding increases ‘willingness to pay’ and contribute to the public good.

Good governance, involving the highest interministerial central body for ‘One Health’ coordination, backed up by legislation and a clear mandate, budget appropriation, resource mobilisation and pilot or model programmes that lead to policy development, provides the optimism for implementing comprehensive operational plans that are vertical and horizontal, national and subnational. These are important institutional drivers and enablers for a sustainable public–private partnership.

Recommendations

Comprehensive rabies control programmes should consider combining human, financial and material resources with other interdisciplinary disease programmes to benefit from synergy and maximisation of shared resources. With the guidance of the World Organisation for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), governments, donors, foundations and other private partners should be mobilised to sustain investment in the control and eventual elimination of canine rabies.

Acknowledgement

We are grateful to all our partners in Bohol, the Philippines, for teaching us most valuable lessons for the sustainable control and eventual elimination of rabies.

References

Catch, inject and release: immunocontraception as an alternative to culling and surgical sterilisation to control rabies in free-roaming dogs

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Summary

Over-abundant populations of dogs can be controlled through culling or fertility control, the latter being carried out by surgical sterilisation or chemical contraception. This paper illustrates recent advances in immunocontraception for wildlife and examines the efficacy, cost and the environmental, social and animal welfare impact of methods to reduce the size of the dog population. The results suggest that immunocontraception is the most humane, effective, publicly acceptable and sustainable method to manage too-large populations of free-roaming dogs.

Keywords

Introduction

Rabies elimination is usually tackled through a combination of public education, mass dog vaccination and dog population management. The latter is achieved by reducing the number of free-roaming dogs through culling or surgical sterilisation. Traditionally, culling has been the most common method used to reduce the size of the dog population. However, this practice has met significant public opposition, due to concerns about the humaneness of the methods employed and the lack of proven effectiveness in controlling dog numbers, or diseases such as rabies. Fertility control, as an alternative to lethal control, is increasingly advocated and employed as a humane means of managing dog populations in the context of rabies control. As a result, surgical sterilisation has been used in rabies control programmes (also called ABC = Animal Birth Control or CNR = Catch, Neuter and Release programmes) in many countries. However, surgical sterilisation is time-consuming and expensive for large-scale applications (11). Recently developed immunocontraceptive vaccines designed for wildlife applications could provide an alternative to culling and surgical sterilisation.

Vaccination campaigns have successfully eliminated rabies in many parts of the world. In some instances this was not achieved, however, because an adequate proportion of dogs could not be vaccinated (12). As inadequate vaccination coverage can reinforce natural disease cycles and promote the endemic establishment of a disease, achieving population immunity is particularly important (4). The empirical and theoretical evidence suggests that adding fertility control to vaccination could be a more efficient method to control wildlife diseases (9, 14, 17), as well as rabies in dogs (2, 15).
New approaches in dog rabies control programmes

The aims of this review were:

– to examine recent developments in immunocontraceptive vaccines to control over-abundant populations of wildlife, in the context of disease control

– to compare the efficacy, the environmental, social and welfare impact, the cost, and the sustainability of culling, surgical sterilisation and immunocontraception to control rabies in free-roaming dogs.

**Methods**

Data on and considerations of the costs and benefits of methods of managing dog populations in the context of rabies control were obtained from peer-reviewed papers, books, published reports and conference proceedings. The following criteria, often used in wildlife management, were applied to compare culling, surgical sterilisation and immunocontraception:

1. **efficacy**
2. **environmental impact**
3. **animal welfare impact**
4. **social impact**
5. **cost**
6. **sustainability**.

**Immuoncontraceptive vaccines**

In the last decade, several contraceptives have been developed for companion and zoo animals. However, most of these drugs are either too expensive or require several doses, often administered at specified intervals; this prevents their use in the developing world where resources are limited and accessing dogs on a regular basis can be difficult. Recently developed immunocontraceptive vaccines seem the most promising candidates for dog population management. These vaccines stimulate the immune system to produce antibodies against proteins or hormones essential for reproduction. Once exposed to the antigen (the vaccine), an animal will usually retain a complement of antibodies to ward off future exposures and thus potentially remain infertile for as long as the antibodies are sustained. This is the principle underlying many vaccines developed to protect against disease.

A new generation of single-dose immunocontraceptive vaccines capable of inducing long-term infertility has been successfully tested on a variety of animal species (3). In particular, gonadotropin-releasing hormone (GnRH) vaccines have been developed for livestock and wildlife applications. GnRH controls the synthesis and secretion of reproductive hormones. Blocking GnRH prevents ovulation and the oestrous cycle in females and the production of sperm and testosterone in males. Studies with several species of mammals showed that a single dose of the GnRH-based immunocontraceptive vaccine GonaCon™ is very effective at inhibiting reproduction for several years. The immune response is achieved by conjugating the peptide GnRH to a mollusc protein carrier. The success of GonaCon™ is due to the unique design of the GnRH-mollusc conjugate coupled with AdjuVac™, an adjuvant containing killed *Mycobacterium avium*.

A single injection of GonaCon™ has been shown to be safe and effective in reducing fertility in feral pigs (*Sus scrofa*), wild horses (*Equus caballus*), white-tailed deer (*Odocoileus virginianus*), elk (*Cervus elaphus*), cats (*Felis catus*) and bison (*Bison bison*), in studies lasting one to six years (6, 10, 13). In female cats, GonaCon™ prevented pregnancy in 87% of animals in the first year, and in 67%, 54%, 33% and 27% of cats in years 2, 3, 4 and 5, respectively (8). In 92% of female wild boar, a single injection of GonaCon™ inhibited reproduction for at least four to six years without physiological or behavioural side effects (10).
Although several studies found no side effects of GonaCon™, others have reported that animals developed palpable, non-painful, injection-site granulomata or sterile abscesses (8). Earlier trials with dogs showed adverse injection site reactions a few weeks after injection, with formation of sterile abscesses and draining tracts at the injection site (7). Following these findings, a new formulation of GonaCon™ was produced with the intention of minimising injection site reaction in dogs, whilst maintaining long-term efficacy. Initial trials on captive dogs in Mexico suggested that, using the latest formulation, adverse effects were less frequent and of a lower intensity than reported in previous studies (19).

The longevity of the effect of GonaCon™ to induce infertility might depend on many factors, including species, age, health conditions, reproductive status, genetic variation in animal populations and exposure to antigens. Understanding the role that these factors play in shaping an individual’s response to immunocontraception will assist in improving fertility control applications for rabies control. More research is also required to confirm that the new formulation is safe and effective in different dog populations.

GonaCon™ is already registered for use in wildlife and will be available at a fraction of the cost of surgical sterilisation. Immunocontraceptives that induce infertility for two to three years will probably cover the entire lifespan of most dogs in the developing world. Immunocontraceptives that can render animals infertile for at least a year could also be used in conjunction with annual rabies vaccinations. As GonaCon™ does not affect parenteral rabies immunisation in dogs (1), rabies and immunocontraceptive vaccines could be administered together, to optimise rabies control.

**Culling, surgical sterilisation and immunocontraception to manage dog populations**

Of the three methods to manage dog populations, culling is the one that has received least attention in terms of costs, impact on population size and rabies incidence, environmental and social impact, and sustainability (Table I).

Culling typically occurs in response to a local rabies outbreak, or when large crowds gather for an international event (such as the South Pacific Games, the Olympics or the celebrations for the Coptic millennium) in areas where dogs pose significant risks for rabies transmission. In these instances, many governments and local authorities implement mass slaughter or poisoning of dogs as a ‘quick fix’ solution. In most cases the effectiveness of culling is not evaluated; local citizens are not consulted or informed about the availability of alternative options, the environmental impact is ignored, even when baits containing strychnine are widely distributed, and the cost is borne by the local authority. Only very recently, thanks to the Internet and to an increased general awareness of animal welfare issues, has the public been able to put significant pressure on governments to halt mass culling of dogs. For instance, in 2008, the plan to kill tens of thousands of street dogs in Kashmir (India) was abandoned following public protest; similarly, in 2011 the Chinese government cancelled a dog cull in Jiangmen City, yielding to public pressure.

From an ecological perspective, there is no evidence that the removal of dogs alone has ever had a significant impact on dog population densities or on the spread of rabies (www.who.int/rabies/animal/dogs/en/index.html). In addition, culling may promote increased immigration, disrupt social organisation and remove vaccinated individuals, all of which make rabies control more difficult to achieve. Studies on the effects of culling on wildlife diseases have suggested that lethal control may cause social disruption and actually result in increased contact rates as animals make long-distance movements, filling the voids left by those that have been removed from the population or re-establishing territories (17). Conversely, fertility control is less likely to cause social disruption as, compared to culling, animal movements are less likely to change following
sterilisation (16). By eliminating reproductive behaviour, fertility control also has the potential to
decrease contact rates, between sexes and between males congregating around a receptive female,
thus resulting in a lower risk of disease transmission (14).

Table I
Six criteria to select dog population control options, based on ecological, ethical and socio-
economic considerations

<table>
<thead>
<tr>
<th></th>
<th>Culling</th>
<th>Surgical sterilisation</th>
<th>Immunocontraception</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Little evidence on the percentage</td>
<td>Empirical and theoretical evidence is available on the percentage</td>
<td>Empirical and theoretical evidence is available on the percentage</td>
</tr>
<tr>
<td></td>
<td>required to achieve a reduction in</td>
<td>of dogs that must be targeted to reduce population size and</td>
<td>of dogs that must be targeted to reduce population size and</td>
</tr>
<tr>
<td></td>
<td>dog population size and rabies</td>
<td>rabies incidence</td>
<td>rabies incidence</td>
</tr>
<tr>
<td></td>
<td>incidence</td>
<td>Lack of sexual behaviour can decrease contact rate and roaming</td>
<td>Lack of sexual behaviour can decrease contact rate and roaming</td>
</tr>
<tr>
<td></td>
<td>Likely to encourage immigration</td>
<td>Can extend lifespan of free-roaming dogs</td>
<td>Can extend lifespan of free-roaming dogs</td>
</tr>
<tr>
<td></td>
<td>and social perturbation and thus</td>
<td>Unlikely to encourage immigration</td>
<td>Unlikely to encourage immigration</td>
</tr>
<tr>
<td></td>
<td>increase contact rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td>Toxins may affect non-target species</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>impact</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Animal welfare</strong></td>
<td>Often carried out with inhumane</td>
<td>Perceived as more humane than culling</td>
<td>Perceived as the most humane of all methods</td>
</tr>
<tr>
<td><strong>impact</strong></td>
<td>methods</td>
<td>Potential surgery-associated complications</td>
<td>Potential injection-site reactions must be evaluated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Social impact</strong></td>
<td>Many ‘stray’ dogs have owners that</td>
<td>Owners are more likely to accept sterilisation than culling</td>
<td>Owners are more likely to accept contraception than surgical sterilisation or culling</td>
</tr>
<tr>
<td></td>
<td>oppose culling</td>
<td>Owners may dislike surgery on welfare grounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culling reinforces the ‘quick fix’</td>
<td>Sterilisation encourages responsible ownership</td>
<td></td>
</tr>
<tr>
<td></td>
<td>solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Not estimated</td>
<td>Variable, from US$ 10 to US$ 52 per dog</td>
<td>Likely to be &lt;$10 per dog</td>
</tr>
<tr>
<td></td>
<td>Includes staff time and safe</td>
<td>Requires specialised staff, drugs and facilities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disposal of carcasses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sustainability</strong></td>
<td>Must be carried out continuously to</td>
<td>More sustainable than culling once a proportion of sterile</td>
<td>More sustainable than culling and surgical sterilisation once a proportion of sterile dogs is achieved</td>
</tr>
<tr>
<td></td>
<td>offset dog population growth</td>
<td>dogs is achieved</td>
<td></td>
</tr>
</tbody>
</table>

Compared to culling, fertility control aims to reduce population size and growth by decreasing birth
rates, rather than by increasing mortality. This has several advantages over culling: treated individuals
remain in the population, thus maintaining density-dependent control on population growth; there are
fewer associated ethical problems, fertility control can increase the lifespan of dogs and both
empirical and modelling studies indicate that fertility control can effectively reduce population
numbers (2, 18).

Many of the advantages of surgical sterilisation are the same as those of immunocontraception
(Table I). However, some of the differences can have profound effects on the implementation of these
methods and ultimately on the success of fertility control to eliminate rabies. For instance, dog owners
may be unwilling to have their dogs spayed or neutered for fear of surgery-associated complications.
This attitude can influence the number of dogs that are brought to clinics by their owners and thus the
proportion of the population that is vaccinated. The main difference between immunocontraception
and surgical sterilisation is that the latter is relatively expensive because it relies on specialised staff,
drugs and infrastructures and is thus unlikely to be as sustainable as immunocontraception.
In contrast, vaccination is less expensive because animals can be released as soon as they have been injected. This is exemplified by data collected by the World Society for the Protection of Animals (WSPA) in 2004 and 2005: in countries where rabies vaccination and surgical sterilisation campaigns were actively promoted, the ratio of dogs sterilised to dogs vaccinated against rabies could be as high as 1:10. This was partly due to the fact that it is quicker and cheaper to inject a vaccine than to carry out surgery on a dog and highlighted the fact that larger numbers of dogs could be sterilised if a contraceptive could be administered together with the rabies vaccination.

The WSPA also estimated that, in 2004 to 2005, the cost of surgical sterilisations in Mexico, Sri Lanka and India was US$ 8 to US$ 23 per dog, including full staffing costs and total operating costs. A more recent estimate indicates that the average total cost of surgical sterilisation is currently US$ 30, varying between US$ 10 and US$ 52 (5). In countries where millions of people live on less than one dollar a day, this cost is prohibitive and is usually met by non-governmental organisations or by local authorities. The cost of surgical sterilisation clearly affects the sustainability of a programme aimed at reducing population size and eliminating canine rabies, although several examples of well-conducted, successful surgical sterilisation campaigns exist. For instance, in large Indian cities, well-coordinated ABC programmes resulted in 62% to 86% of dogs being sterilised (15, 18).

**Conclusions**

Of all the methods available to reduce dog population size, culling should be discarded on scientific, social, ethical and economic grounds. The general public antipathy towards this method, coupled with growing awareness of alternative options and increased information flow through the Internet, are likely to make it very difficult for public authorities to justify its use.

On the other hand, fertility control, achieved through surgical sterilisation or chemical contraception, offers a long-term, effective and publicly acceptable method of reducing the size of dog populations in the context of rabies control. As immunocontraceptives, particularly for large-scale applications, are likely to be significantly less expensive than surgical sterilisations, programmes based on immunocontraception can make better use of the funding available for dog population management and rabies control. Given the costs associated with the ‘catch-neuter-release’ approach that relies on surgical sterilisation, a ‘catch-inject-release’ method based on immunocontraception thus appears to be the most efficient option to manage over-abundant populations of dogs and to control zoonoses (11).

Before immunocontraceptives become available for large-scale applications, a number of issues must be addressed. Although preliminary data indicate that the new formulation of GonaCon™ is promising, its long-term effectiveness in dogs must be evaluated. As the immune response to vaccines may change dramatically in different human and animal populations, trials must be carried out in several countries to confirm the preliminary results of the study conducted in Mexico. Provided that GonaCon™ renders a relatively high (>75%) proportion of dogs infertile, for at least a year, and that the side effects, if present, are acceptable on welfare grounds, large-scale studies can be initiated to determine how immunocontraception can assist with rabies elimination.

A recent study (2) suggested that, when fertility control was added to vaccination, the control rate and duration required for rabies eradication were reduced by about half, supporting similar predictions from wildlife disease models (17). Further work is required to improve our understanding of dog ecology and parameterise location-specific models, which could be used to inform management plans.
Once the long-term effectiveness and potential side effects of an immunocontraceptive have been evaluated and found satisfactory, other challenges remain. These involve answering certain questions on a context-specific, theoretical, as well as empirical, basis.

- What is the proportion of dogs to be vaccinated and rendered infertile to achieve rabies elimination within a set time frame?
- What is the frequency of application of vaccination (rabies and contraception) required to achieve rabies elimination within a set time frame?
- How do we measure the impact of immunocontraception and vaccination on rabies elimination, i.e. a decrease in the number of bites or in the number of human deaths?
- What are the costs of sustaining a dog population control programme based on vaccination and immunocontraception and who will sustain these costs?

Other ecological questions are also important, such as ‘What are the effects of immunocontraception on dogs’ social and spatial behaviour?’, ‘Does immunocontraception reduce dog-to-dog contact rate?’ and ‘Does immunocontraception increase lifespan?’ Only by addressing these issues will we understand and be able to exploit the effect of immunocontraception on zoonoses: this knowledge will ultimately provide a powerful, humane, effective and publicly acceptable tool for rabies elimination.

**Recommendations**

Culling as a method to reduce the population size of free-roaming dogs and decrease rabies incidence has unacceptable social and welfare costs, can have a negative environmental impact and cannot be justified in terms of efficacy and sustainability.

Fertility control carried out through immunocontraception is less expensive than surgical sterilisation and can provide a safe, humane, socially acceptable alternative to culling or surgical sterilisation.

More research on immunocontraception should be carried out to determine how this method could be integrated with rabies vaccination to eliminate canine rabies.

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**References**


Mainstreaming rabies prevention and control at the national level: a focus on the role of national Veterinary Services

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Summary

Rabies, like many other zoonotic diseases, calls for both the animal health and human health professions to take equal responsibility for its prevention and control. However, in many countries, there is still a never-ending debate between the Ministries of Health and Agriculture as to who is responsible for what. The end result of many of these debates is that dog owners are perceived as being responsible for having their animals vaccinated or preventing them from coming into contact with infected animals. Should this not be attainable, then the human health profession must take on the costly responsibility for treating the unfortunate victims of the disease. Such a perception inevitably results in humans continuing to contract and die from this disease, due to exposure to an unattended, non-vaccinated canine population – worldwide, the most important species responsible for transmission of the disease to humans. The primary task of the animal health profession is to create an immune buffer between the animal source and humans through a rigorous and sustainable strategy of vaccinating the canine population. It has been proven in many countries that, by maintaining vaccination coverage of at least 70% to 75% of the dog population, the number of humans contracting the disease decreases exponentially. To enable countries’ Veterinary Services to accept and fulfil this primary responsibility, they must be given the capacity and capability to do so.

The paper will outline some of the critical and core responsibilities and actions that need to be considered and put into operation by Veterinary Services to effectively control the disease and enable them, together with their human health counterparts, to deliver assurances to the human population that eliminating rabies is considered a public good, and is being well and effectively attended to within the national borders of the country.

Keywords


Introduction

At the 2007 World Organisation for Animal Health (OIE)/World Health Organization (WHO) Global Conference on Rabies, OIE Director General, Jean Blancou, stated in his opening address that human rabies ranks seventh among infectious diseases causing deaths in humans, but that these human deaths could be avoided. He noted that the burden of rabies is not so much a threat to the rural economy but rather that its elimination will essentially benefit human health services, which should
share in the cost of its elimination (2). In sharing responsibility, both the Veterinary Services of a country and its Ministry of Human Health become prime players in delivering what is expected of a primary service for the public good. The OIE has stated on many occasions that the delivery of Veterinary Services is a global public good (8, 13). However, for a rabies-free environment to be a public good, it should be non-rival and non-exclusive, to enable all citizens in a country to share equally in the benefits.

In many countries, rabies vaccination is not free and Ministries of Agriculture and Health have to compete with other national disease-related priorities, such as human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) and foot and mouth disease, to try to secure funding for rabies control and prevention. This often results in insufficient funding – partly due to the lack of efficient cost estimates for all direct and indirect aspects of rabies control and partly due to the perceived lack of return on investment. The potential savings in human lives due to efficient control of rabies remain difficult to estimate or to reconcile with any allocated budget (5, 6, 7).

The question might well be asked: why, then, after being known and feared by mankind for more than 4,000 years, does rabies still remain the number-one killer infectious disease in humans? It is common knowledge that rabies may be the oldest infectious disease known to humanity. As early as 2300 BC, dog owners in the Babylonian city of Eshnunna were being heavily fined for deaths caused by their dogs biting people. As early as 500 BC, there were even special rabies gods: one to prevent rabies (Arisaeus, son of Apollo) and one to heal rabies (Artemis). The disease was known and feared by everyone, killing people in villages and in large cities, such as Paris in the early 1600s, as well as Madrid, London and, later, cities in America and South America (1). Even after Pasteur, a chemist from Paris, successfully applied a crude rabies vaccine to young Joseph Meister for the very first time in 1885, rabies continued to remain a mysterious killer disease. Even today, rabies is reported to claim nearly 60,000 to 70,000 lives a year – more than any other infectious disease known to humanity (5).

Another question might well be asked: why do other animal diseases posing a threat to human health and well-being – but with a much lesser mortality rate – receive more prominence in the popular press and cause more hysteria and pressure on governments to protect human health? Animal disease-related events that covered the front pages of international newspapers during the past ten to 15 years have included the outbreak and further spread of ‘mad cow disease’ or bovine spongiform encephalopathy (BSE) in the United Kingdom (UK); highly pathogenic H5N1 avian influenza, which spread over five continents in a very short time, causing the threat of a possible human pandemic; the recent outbreak of H1N1 influenza and an outbreak of Ebola Reston virus in the Philippines. These are just a few examples of the strong link between human and animal health and causes for global concern. In almost all these instances, the main thrust was the general fear of a global human pandemic occurring as a result of the presence of these diseases in animals. It was thus not surprising that the international donor community, urged on by international organisations, such as the OIE, Food and Agriculture Organization of the United Nations (FAO) and WHO, reacted swiftly by mobilising and coordinating their efforts to raise substantial financial support to strengthen the capacity of countries to face these threats. This was especially evident during the height of the highly pathogenic avian influenza (HPAI) epidemic. An unprecedented amount of money was pledged and made available to prevent a possible global human pandemic, should the disease spill over from its animal source to a naive human population (9).

Sadly, as one of the oldest known diseases occurring primarily in animals, being responsible for more deaths in humans than any of the other known zoonoses, and by far exceeding the sum total of recorded human deaths from BSE, HPAI or the recent H1N1 influenza outbreak, rabies seems to be either forgotten or pushed to the back of the queue of animal disease priorities. Rabies still causes the deaths of thousands of people annually, on continents such as Asia and Africa, where insufficient means are available to create an effective immune and protective barrier between humans and the
animal source of the disease (3, 4). Scientists and other experts have offered many reasons for the perceived inability or reluctance of governments to react and mobilise resources to fight rabies. One reason cited is that there is very little financial return on the investments of governments into rabies control programmes, such as pre- and post-exposure treatment of human victims, or controlling the disease at the animal source by implementing rigorous and effective vaccination programmes (5).

In a recent editorial by Dr Bernard Vallat, Director General of the OIE, it is estimated that just 10% of the financial resources currently used for post-exposure treatment of rabies victims would be sufficient to enable national Veterinary Services throughout the world to eradicate rabies at the animal source and, in doing so, prevent human cases of the disease (13).

**Cooperation between the human and animal health professions**

The primary task of the animal health profession, and especially that of Veterinary Services, is to create an immune buffer between the animal source and humans through a rigorous and sustainable vaccination strategy of the main animal vector; namely, dogs. It has been proven in many countries that, by maintaining vaccination coverage of at least 70% to 75% of the canine population in a country, the number of humans contracting the disease would decrease exponentially. To enable the Veterinary Services of countries to accept and fulfil this primary responsibility, they need to be given the resources to do so. However, even if enough money was re-directed to the purpose of rabies control at the animal source by the Veterinary Services, would it actually result in an effective and coordinated effort to really control the disease? In many countries, there still appears to be a never-ending debate between the Ministries of Health and Agriculture as to who is responsible for what. The result of many of these debates is that dog owners are perceived as being responsible for having their animals vaccinated or preventing them from coming into contact with infected animals. Should this not be attainable, then the human health profession is regarded as having to take responsibility for treating the unfortunate victims of the disease. Such a perception inevitably results in humans continuing to contract and die from this disease, due to exposure to an increasing, non-vaccinated canine population – globally the most important species for transmission of the disease to humans. Rabies is a disease that calls for the equal involvement of both human and animal health professions.

Increasing the capacity of a country’s national Veterinary Services does not always imply simply making more money available to control the disease. Only by fully accepting the core responsibilities of controlling the disease in animals, and taking stock of what is really needed to achieve effective control, will the Veterinary Services, and the veterinary profession at large, be able to claim that they have done their part to reduce and finally eliminate human cases of the disease. In the end, the success of rabies control in a country is measured by the decrease in human fatalities from the disease, not by how many dogs were or were not vaccinated.

The urgent need for closer cooperation and inter-sectoral liaison for rabies prevention and control has been pledged and emphasised since 1928 in several Resolutions of the OIE, by researchers, at almost every national and international conference on rabies and in numerous publications. However, the issue of rabies control seems to be a source of diverse opinions. Are we talking about rabies control in animals, rabies control in humans or just rabies control? The foremost priority should be, wherever possible, the establishment of an immune canine population to at least the level of, but preferably above, the acceptable threshold level to minimise or protect against the spillover of disease from the animal vector to humans. To argue and debate the cost of post-exposure prophylactic (PEP) treatment in humans; to build models of ideal ways to attract and maintain human sensitivity on the need for prevention at the animal source or to debate when and for whom vaccination should be free, might all make relative contributions to the eventual success of a national control strategy for rabies – but only if all such good intentions are put into practice by a rigorous and sustainable
Strategies today and tomorrow at the animal source vaccination programme (5, 6, 7). However, to achieve such an ideal, the Veterinary Services of a country, in consultation with their counterparts in the human health environment, should carefully consider all aspects of planning an effective national rabies control strategy.

Although rabies is a notifiable disease in most of the 178 Member Countries of the OIE, systematic control programmes are in force in a relatively limited number of countries – most obviously in those countries where there is an urgent need for one (11, 13). Success stories are known in areas where rigid vaccination and control programmes have been initiated, such as South America, the Philippines, Kwa-Zulu Natal in South Africa, Europe and North America. However, the most common approach still seems to be restricted to post-outbreak emergency responses with the general perception that, if there are no outbreaks, there is no reason for action.

The main focuses for mainstreaming the role of Veterinary Services in rabies control

Liaison with human health professionals

If we accept that the control of rabies is a multidisciplinary responsibility, and wish to promote the need and urgency for national animal and human health professionals and administrators to talk to each other and to plan together for a national rabies control strategy, then what should they talk about and what should be the baseline for successful coordination? The following aspects should at least be considered:

– having detailed budgets and reliable real-time data on the rabies situation in the country
– determining who should do what and when
– budgets (current and planned) should be compared with the original rationale for these budgets, what was really intended and what has been achieved with the current allocations
– agreement on the need and commitment to control and prevent rabies at the animal source, and comparing costs to enable a reduction in the costs for PEP treatment – taking into account the direct and indirect costs of the disease
– agreement on achievable and realistic goals and timelines
– agreement on budgeting for sustainability
– agreement on avoiding a top-down approach, and instead involving local authorities and communities.

Aspects of planning a national rabies control strategy

During the planning process of a national rabies control strategy, some critical aspects related to rabies are sometimes considered common knowledge, or so obvious that they are often excluded from or not considered in their real context during the planning process. Some of these considerations can include the following:

– the cost of rabies prevention in animals is more than simply the cost of vaccine for the animals
– we need to know the status of rabies in the country concerned. Are there reliable and updated surveillance data available?
– we should know the size of the various dog population(s) in the country (owned, stray, feral)
– we should know the dog population turnover to ensure maintenance of the 70% coverage
– we should know the logistical costs of administering vaccine to every dog in the villages
– we should know if samples can be taken correctly and correctly packed and secured for dispatch
– we should know if the sample can be transported to and reach the laboratory without delay
– we should know if we can have confidence in the results of the laboratory tests
– we should know if the result of the test can be communicated back to the source without delay
– we should know, if PEP treatment is indicated, if and where it will be available – and if the patient can be transported to the treatment facility.

Some considerations for establishing a budget for a national rabies control programme

The Veterinary Services of countries are often restricted by budgetary prescripts for budget submissions. The way in which budgets need to be formulated for submission to Ministries of Finance often requires a specific format and criteria for listing the needs of the Veterinary Services. Related aspects of a rabies control programme might get spread among, and very often diluted in, sub-categories of the budget submission without allowing a coherent expression of the total needs of a sustainable rabies control programme. To ensure that the Ministry of Finance ‘buys into’ the entire programme, it is essential that the total needs are expressed in one disease-specific package, expressing not only its immediate needs but also provision for it to remain sustainable in the future and to achieve its objective. Some of the following should at least be taken into consideration:

– vaccine costs – the costs of free vaccine to all or to a selected target community, or subsidised vaccine costs
– the costs of ongoing surveillance of the disease
– the costs of sample collection
– the costs of dispatching samples
– the costs of examining samples and having access to diagnostic facilities
– the costs of routine vaccination and emergency vaccinations as a risk mitigation measure
– the costs of dog population control strategies, where indicated
– the costs of an ongoing communication programme
– the costs of monitoring and evaluating the national control strategy
– the costs of maintaining and sustaining the programme to ensure at least 70% coverage of the target population.

Some considerations when planning a national rabies control programme

If there is agreement within the Veterinary Services and between the Veterinary Services and the Ministry of Human Health for a national rabies control programme, the Veterinary Services should (after consideration of the budgetary implications and the need for sustainability) formulate a detailed programme and compile a detailed budget that will enable all stakeholders to support the proposal and establish an effective and user-friendly communication and awareness programme. During the planning process, some or all of the following should at least be considered:

– a problem statement – so that everyone knows what the situation is
– a decision on what needs to be achieved in the short and in the medium term
– a strategic plan – to determine what human and physical resources will be needed
– training needs and how they will be addressed and sustained
– outbreak investigation procedures
– disease reporting and follow-up
– how and when will the programme be implemented – i.e. in what time frame and how often should it be repeated?
– legislative framework – is there sufficient legal authority and support to implement the control programme?
– the need for a disease-specific surveillance programme or one in collaboration with other existing programmes of the Veterinary Services
– diagnostic capability and needs – are they sufficient in terms of access and rapid response?
– emergency preparedness and response needs and estimated costs for emergency risk mitigation measures
– programme monitoring – the way it will be conducted and audited to ensure that the Ministry of Finance, other Ministries and stakeholders continue to support the programme, but also, very importantly, that dog owners also ‘buy into’ the programme.

**Assistance available from the World Organisation for Animal Health for rabies prevention and control**

Guidance and help available to Member Countries to implement rabies control are not restricted to the chapter in the OIE *Terrestrial Animal Health Code (Terrestrial Code)*, outlining the international standards for rabies control. In planning their rabies control programme, countries can benefit from a variety of relevant standards, guidelines and general documentation from the OIE which will assist them in mainstream rabies control at the national level. As well as the rabies-specific chapter in the *Terrestrial Code*, there are also other horizontal chapters that directly and indirectly give further guidance, such as the *Terrestrial Code* standards on disease notification procedures, surveillance guidelines for animal diseases, guidelines on import risk analysis and certification, the requirements for the delivery of Veterinary Services, stray dog management and the disposal of dead animals (14). There are also standards on diagnostic tests and rabies vaccines outlined in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)*, while guidelines on veterinary legislation are available on the official OIE website. Further assistance is available from the network of OIE Reference Laboratories and Collaborating Centres (12). The official OIE website also contains cross-references and links to other rabies-related websites, such as the Global Alliance for Rabies Control and WHO websites (www.rabiescontrol.net).

Realising that more than 70% of its 178 Members are either developing or transitional countries that are in urgent need of guidance to effectively control animal diseases and zoonoses, including rabies, the OIE set itself an optimistic goal, to assist at least 120 of its Member Countries to enter the ‘Pathway for Good Veterinary Governance’. Expert teams, trained by the OIE, have, to date, completed 102 assessments of the status of the delivery of Veterinary Services of Member Countries, and can advise them on how to address the gaps to achieve good veterinary governance and thus effectively control important animal diseases, such as rabies. Member Countries who have not yet requested an evaluation of the performance of their Veterinary Services (PVS evaluation) would benefit from such an evaluation as it also assists them to identify possible gaps in their service delivery which might hinder the implementation of an effective and sustainable national rabies control programme. Following the PVS evaluation by an OIE expert team, a Member Country can also request a Gap Analysis by OIE experts to assist them in compiling a complete budget for mainstream rabies control at the national level (15).
The OIE, together with FAO, has made available an extensive publication on good veterinary governance, to further guide countries in need (10). However more importantly, in terms of global rabies control, the OIE, with the assistance of donor funding, has established a World Animal Health and Welfare Fund, from which funds can be made available to further advance the OIE ideal of good veterinary governance by its Members. The OIE has also urged the donor community to allow the substantial funding that was made available to address the HPAI human pandemic threat to be used for the control of other equally important zoonotic diseases, such as rabies.

The need for closer cooperation and collaboration and the importance of confirming their international role as primary participants in combating important diseases threatening human and animal health were publicly acknowledged by the OIE, FAO and WHO, when they recently issued a joint statement confirming this commitment. In this statement, the need for joint efforts at the regional and national levels is accepted, with the aim of obtaining deeper and sustainable political support for the integrated prevention of diseases and mitigation of the effects of high-impact pathogens of medical and veterinary importance. The three organisations also confirmed the need for the joint development of effective interventions to ensure coherent action, as well as awareness among the general public and policy-makers of the risks of and appropriate actions needed to minimise human infection by pathogens of animal origin. Prevention of the emergence and cross-border spread of human and animal infectious diseases was acknowledged as a global public good, with benefits which extend to all countries, people and generations. The tripartite partners encouraged international solidarity in the control of human and animal diseases, while providing international support to Member Countries requesting assistance with human and animal disease control and eradication operations (10). It is sincerely hoped that this common commitment by the three major international players will filter through to and be equally applied at the regional and national level to control rabies.

Conclusions and recommendations

The Veterinary Services of countries should accept that the occurrence of each rabies case in humans, especially if the primary source of such a case was a bite by or contact with a rabid dog, reflects on the ability of the Veterinary Services to control the disease. Rabies is and will remain the primary responsibility of the veterinary profession to control at the animal source by creating an immune buffer between the animal source of the disease and the human victim, through a rigorous and sustainable vaccination programme. There are already good examples of success stories of inter-sectoral cooperation in several countries of the world, where it has proven possible to bring rabies under control or, in some instances, to totally eradicate the disease. Veterinary Services should not merely accept that, where they fail to control this dreadful disease, there is always PEP as a back-up strategy. By mainstreaming rabies prevention and control, Veterinary Services should strive to collaborate with other disciplines to make and maintain rabies control as a public good – to make it truly non-rival and non-excludable for all.

References

OIE activities to support sustainable rabies control: vaccine banks, OIE twinning, and evaluation of the performance of Veterinary Services

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Summary

Rabies causes an estimated 55,000 deaths worldwide in developing and in-transition countries, a large proportion of these deaths occurring in children. Successful rabies prevention and control requires the collective efforts of many people. The focus should be on containment and the eventual eradication of rabies at the animal source of the disease, primarily dogs. The World Organisation for Animal Health (OIE) strategies emphasise the ‘One Health’ approach, including building the capacities of Veterinary Services (VS) to support public and animal health, and working with a range of international and national organisations. Due recognition should be given to both immediate actions and approaches that support long-term maintenance of and improvements to rabies control strategies. Three examples of OIE initiatives are provided, which support a sustainable approach. The Performance of Veterinary Services tool (PVS tool) for the evaluation of VS, PVS Gap Analysis and PVS follow-up aim to strengthen good governance, building on technical and management capacities and legislation to support continuous improvements in these areas. Improving VS, including public and private components, will facilitate the application of knowledge and skills to help control zoonoses such as rabies. Parenteral rabies vaccination of dogs has been the method of choice but there are limitations to this approach. Since oral vaccination has successfully been used in certain wildlife species, it is considered worthwhile to promote research on suitable oral vaccines for dogs as well, to complement parenteral vaccination and other management techniques. The OIE plans to establish a rabies Regional Vaccine Bank Pilot Programme in Asia and collaborate with other partners involved in rabies control. ‘Twinning’ arrangements provide links between an OIE Collaborating Centre (the parent) and a National Centre (the candidate). These seek to improve expertise and diagnostic capacities. Current ‘twinning’ arrangements for rabies are established between the United Kingdom and the People’s Republic of China, South Africa and Nigeria, and Germany and Turkey. These OIE approaches create opportunities to overcome a number of the key challenges of rabies control in a sustainable manner.
Introduction

Rabies is considered one of the most lethal zoonotic diseases and kills more people each year than severe acute respiratory syndrome (SARS), H5N1 and dengue fever, combined (1). It causes an estimated 55,000 deaths worldwide in developing and in-transition countries, a large proportion of these occurring in children. The epidemic is so severe that one child dies every ten minutes from this disease. In 99% of human cases, the cause is the bite of infected dogs (9). Infection of humans is almost always fatal once signs of the disease occur (8).

Rabies places a dreadful economic burden on the populations where it strikes, in addition to the suffering it inflicts on victims and survivors (4). The annual global expenditure for rabies prevention is, by conservative assessment, well over US$ 1 billion. This expenditure, as well as the frequency of post-exposure prophylaxis, is expected to rise dramatically as all countries replace nerve tissue-vaccines by modern, safe and highly potent rabies vaccines developed in cell cultures or embryonated duck eggs (8).

Of the financial resources currently used to treat people bitten by potentially rabid dogs, it is estimated that just 10% would be sufficient to enable national Veterinary Services (VS) throughout the world to eradicate rabies at the source in domestic animals and so prevent almost all human cases (7). Parenteral rabies vaccination of dogs has been the method of choice but there are limitations to this approach. Since oral vaccination has successfully been used in certain wildlife species, it is considered worthwhile to promote research on suitable oral vaccines for dogs as well, to complement parenteral vaccination and other management techniques.

The culling of animals that are potential vectors cannot be considered the priority method for control and eradication. It has been proven by research that, in those parts of the world where dog rabies is present and comprehensive dog vaccination programmes have been carried out, in conjunction with an improvement in educational awareness and the availability of human vaccines, deaths from rabies have been reduced to zero (4). A rabies control strategy cannot be effective without the support of many different partners coordinated by the authorities, including the animal health services, environmental officers and the police force, and without the support of local and municipal authorities, non-governmental organisations (NGOs) and dog owners (7).

A key direction of the World Organisation for Animal Health (OIE) 2011 to 2015 Strategy is ‘One Health’ to support the reduction and management of risk at the animal/human/ecosystems interface. These strategies emphasise addressing ‘One Health’ issues, including rabies; building the capacities of VS to support public and animal health, the development and implementation of scientifically based standards, and working with a range of international and national organisations. OIE strategies support short term actions and longer term approaches with the objective of facilitating long-term maintenance and improvements to rabies control programmes and ensuring sustainability.
Performance of Veterinary Services Pathway

One of the main levers for providing practical help to strengthen VS is to put in place sound governance and structural and procedural arrangements, using the PVS Pathway: PVS Tool, PVS Gap Analysis (GA), and PVS follow-up. It is a continuous process which aims to sustainably improve the compliance of VS with international standards (2), and can be represented by the following diagram.

Fig. 1
The Performance of Veterinary Services Pathway

The first step of the PVS pathway is OIE PVS evaluation, or the ‘diagnosis’. This involves a country voluntarily requesting an OIE-trained and certified expert team to conduct a two-to-three week mission to comprehensively evaluate all aspects of its VS, using the OIE Tool for the Evaluation of Performance of Veterinary Services (OIE PVS Tool). The tool measures four fundamental components of national VS: human, physical and financial resources; technical authority and capability; interaction with stakeholders; and access to markets (1). It is also a mechanism to promote a culture of awareness and sustained interactions with the public/private sectors. The PVS evaluation has been a resounding success with more than 100 countries voluntarily taking this step to date (see Table I).

The PVS evaluation then forms the basis for the second step, the voluntary PVS Gap Analysis mission, or the ‘prescription’. The PVS Gap Analysis is a follow-up activity to analyse the results of the evaluation and helps to identify priorities for action and prepare investment programmes for national/international support. Whereas the PVS evaluation focuses on independent and objective assessment against international standards, the PVS Gap Analysis mission uses a participatory approach to facilitate planning that the country in question can ‘own’, based on a careful integration of national priorities and the PVS evaluation results and international standards.
Table I
State of play of Performance of Veterinary Services Evaluation and Gap Analysis, as of August 2011

<table>
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<th>OIE Regions</th>
<th>OIE Members</th>
<th>PVS evaluations requested</th>
<th>PVS evaluations completed</th>
<th>Gap analysis requested</th>
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<td>11</td>
<td>6</td>
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<td>15</td>
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<td>Europe</td>
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<td>12</td>
<td>11</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>178</td>
<td>116</td>
<td>104</td>
<td>67</td>
<td>42</td>
</tr>
</tbody>
</table>

The third stage, dubbed the ‘treatment’ phase, incorporates the progression from the planning of PVS Gap Analysis through to resourcing and implementation within the country to strengthen VS. A suite of support and activity is available to this end (1). Specific assistance from the OIE includes the transformation of the results of Gap Analysis into VS Strategic Plans, with pilots being undertaken in Vietnam and the Philippines, under the Australian Agency for International Development (AusAID) Programme for Strengthening Veterinary Services (PSVS).

The final phase of the PVS Pathway incorporates a monitoring and evaluation component to assess progress along the PVS Pathway via a PVS ‘follow-up’ evaluation. The PVS tool is again used to provide consistent measurement against the original PVS evaluation (‘diagnosis’) benchmark, taking into account the planning, resourcing and implementation activities that have taken place since. Following this, a further Gap Analysis planning mission can be undertaken and thus a ‘cycle of continuous improvement’ can be developed for sustainable and continuous VS strengthening. The beginning of a new phase or cycle of the PVS pathway is estimated to be approximately four to five years, but this may be shorter or longer, depending on case-by-case factors, such as internal planning cycles and an evolving VS context and needs (1).

Given that VS are at the front line of animal health, including zoonotic activities, ongoing improvements can support sustainable rabies prevention and control systems.

The PVS components will continue to be expanded to cover new areas, e.g. wildlife management services relevant to animal health, and ‘One Health’. PVS follow-up activities will also ensure that countries are up to date with the newest developments.

Rabies control programmes are a major financial challenge for many countries as the costs, especially vaccination costs, are very high. It is therefore important to encourage research and industry to develop vaccines that will confer long-term immunity, thereby eliminating the need for booster vaccinations. In this context, the quality standards for the production of diagnostic tests and vaccines for rabies contained in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual) are currently being updated to take into account the very latest scientific developments.

**Vaccine bank**

Successful rabies control and eradication requires management at the animal source with the focus on containment and eventual eradication, especially in dogs. The control and elimination of rabies in dogs through vaccination remains the only cost-effective way to sustainably protect humans from contracting the disease. Massive culling of dog populations or wildlife, as an isolated, interim or
emergency control measure, is neither sustainable nor scientifically supported for efficiently controlling or eliminating dog-mediated rabies (12). The OIE is of the view that oral vaccination of dogs, in association with parenteral vaccination of dogs (and human prophylaxis), should be promoted together with multi-sectorial/disciplinary coordination. Baits, if successful, could improve vaccine coverage in certain situations. In many European countries, a 95% reduction in animal cases (mainly foxes) has been reported over the past nine years, following the massive use of oral immunisation techniques for foxes and dispersal of millions of vaccine baits since 1989 (5).

The OIE has initiated the establishment of vaccine banks for avian influenza and foot and mouth disease. With financial support from the European Union, and under the framework of the regional cooperation programme on Highly Pathogenic Emerging and Re-emerging Diseases in Asia (HPED programme), the OIE will create a rabies Regional Vaccine Bank in Asia and collaborate with other partners involved in rabies control. A pilot activity will be implemented through the OIE Sub-Regional Representation for Southeast Asia (SRR-SEA) in Bangkok, Thailand. The regional rabies vaccine bank will enable the rapid supply of emergency stock of vaccines to eligible countries, to vaccinate animal populations at risk and to progressively achieve eradication wherever possible, within the framework of agreed national vaccination strategies. (Asian countries eligible for funding at the country level are: Afghanistan, Bangladesh, Bhutan, Cambodia, the People’s Republic of China (PRC), India, Indonesia, the Democratic People’s Republic of Korea, Laos, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, the Philippines, Sri Lanka, Thailand and Vietnam.) The vaccine would comply with the relevant international standards, such as the OIE international standards described in the latest version of the Terrestrial Manual, Chapter 1.1.8.: ‘Principles of veterinary vaccine production’ (10). The rabies vaccine production facility(ies) would also meet the requirements for Containment Group 3 pathogens, as outlined in Chapter 1.1.2. of the Terrestrial Manual (7, 9). Leverage to support vaccine supply by others is also an objective.

The OIE has also invited vaccine manufacturers to come forward with proposals for additional possible pilot projects (including field studies), which would use oral vaccination of dogs, and proposals for field tests in a limited number of Asian countries (where possible) (11).

The next steps for the OIE are establishing the rabies vaccine bank after finalising its form, the vaccine requirements, the criteria for use and modus operandi, and discussing with partners the potential pilot programme objectives, expected benefits and methodologies.

In Southeast Asia, the new AusAID-funded Stop Transboundary Animal Diseases and Zoonoses (STANDZ) programme (2011 to 2016) will use the ‘One Health’ approach to support countries in the development and establishment of cross-sectorial control strategies for rabies. The STANDZ is managed by the OIE SRR-SEA and will operate in Association of Southeast Asian Nations (ASEAN) countries, (and in the case of Foot and Mouth Disease with PRC), but with close links to other countries in the Region where the OIE SRR SEA manages other projects, for example the HPED Programme.

**Twinning**

Twinning is integral to capacity-building for VS and has the objectives of improving the expertise and diagnostic capacity in developing countries, meeting OIE standards and, in the case of some institutions, becoming OIE Reference Laboratories and Collaborating Centres.

The ‘twinning arrangement’ is a link between an OIE Reference Laboratory or Collaborating Centre (Parent) and national laboratory or centre (Candidate) and aims to improve expertise and diagnostic capacity in the candidate, with the eventual aim of providing support within the region and reaching OIE standards. It improves the capability and access of Member Countries to rabies diagnosis and scientific expertise in some regions of the world (12).
The (disease-based) OIE Reference Laboratories are designated to pursue technical and scientific issues relating to a named disease or topic and function as centres of expertise and standardisation of diagnostic techniques. The mandate of (competence-based) OIE Collaborating Centres is to operate as centres of research, expertise, standardisation and dissemination of techniques; provide technical advice and training; develop new techniques and procedures; publish and disseminate useful information; and place expert consultants at the disposal of the OIE. The seven OIE Reference Laboratories for rabies are located in the United States (USA), Canada, France (two laboratories), Germany, South Africa and the United Kingdom (UK). They are the:

- Centre of Expertise for Rabies, Canadian Food Inspection Agency (CFIA/ACIA) (Canada)
- Agence nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (Anses) (two) (France)
- Institute for Epidemiology, Friedrich-Loeffler Institut (Germany)
- Onderstepoort Veterinary Institute (South Africa)
- Virology Department, Animal Health and Veterinary Laboratories Agency (UK)
- National Center for Zoonotic, Vector-borne and Enteric Diseases Centers for Disease Control and Prevention (USA).

Current ‘twinning’ arrangements for rabies have been established between the UK and PRC, South Africa and Nigeria, and Germany and Turkey. The collaboration between the UK and PRC, for example, has indicated that the quality of rabies vaccines used in animals cannot fully eliminate rabies from the dog population. Thus, its priorities are the following: the implementation of diagnostic testing for rabies; validation of in-house diagnostic tests for rabies; participation in proficiency schemes and ring trials for internationally approved diagnostic tests for rabies; epidemiological surveys of rabies in humans and animals; the development of oral recombinant vaccines for dogs; evaluation of vaccination coverage in community-owned dogs; studies of vaccine-elicited immunity in community-owned dogs; and assessment of rabies vaccine quality for animal use (3).

The collaboration between Germany and Turkey established the phylogeny of the rabies virus from the Middle East, harmonised and standardised specific rabies standard operating procedures (SOPs) in 2009, conducted the first Turkish national fluorescent antibody test ring trial in 2009, and initiated bat rabies surveillance in Turkey in 2010 (6).

Conclusions

The three activities described above seek to provide examples of short-, medium- and long-term support for rabies prevention, control and eradication. The PVS aims to strengthen national VS which can provide a buffer between the animal source of the disease and human infection. The OIE rabies vaccine bank will pilot oral vaccination programmes in cooperation with partners. Twinning arrangements enhance the skills and knowledge of scientists and technicians in developing and in-transition countries.

Recommendations

The OIE activities are global public goods; that is, goods whose benefits extend to all countries, people and generations. By recognising the global public good argument and implementing OIE good governance arrangements, sustainability of rabies activities will be realised.
References


Summary

Bohol Province was the region with the fourth-highest number of human rabies deaths in the Philippines before the implementation of the Bohol Rabies Prevention and Elimination Program (BRPEP). In line with the National Rabies Program goal of eliminating rabies by 2020, the BRPEP was initiated in 2007 with the goal of building a sustainable programme to prevent human rabies by eliminating rabies at its source, dogs, by 2010. The intersectoral BRPEP, managed by a council led by the Governor, integrated the agriculture, public health, education, environment, legislation and local government sectors. The programme included: increasing community involvement; dog population control; mass dog vaccination; improving dog-bite management; veterinary quarantine; diagnostics, surveillance and monitoring. Funding came from the government, dog owners, and partner non-governmental organisations (NGOs). Community volunteers facilitated the institution of the programme. Dog population surveys were conducted to plan for sufficient resources for dog vaccination. Two island-wide mass vaccination and catch-up campaigns were conducted. Dog registration was implemented, including a small fee that was re-invested for programme sustainability. Children were educated by introducing rabies prevention modules into all elementary schools. Existing national, provincial and municipal legislation strengthened the enforcement of activities. A community awareness survey was also conducted. Two mass vaccination campaigns conducted in 2007 and 2008 successfully registered and vaccinated 44% and 70% of dogs. The 2009 awareness survey revealed >90% awareness of rabies and its transmission; 89% knew of the BRPEP and thought it was good for their community, and 73% of households no longer allowed their dogs to roam. Registration fees collected during the first two years totalled US$ 105,740, approximating the annual programme cost. These were re-allocated back into the community to sustain the programme. Between October 2008 and November 2010, no human or animal cases were detected by the provincial surveillance system. A suspected human case and a confirmed dog case were readily detected in November 2010 and April 2011, respectively. Rapid case detection prompted quick response and containment. The success of the programme was achieved through empowerment of the local communities and the use of the One Health inter-sectoral approach to rabies control, through the joint efforts and shared resources of local and national government, and
non-government partners. The fact that the number of human deaths has dramatically decreased and surveillance has increased indicates that the programme has been successful.

**Keywords**


**Introduction**

The province of Bohol is the tenth-largest island in the Philippines, with a total land area of 411,726 hectares. It has 47 municipalities and one city with 1,109 barangays (villages). Aside from the main island, it has 81 offshore islands and islets with 30 coastal municipalities and 304 coastal barangays. The human population is 1.2 million.

In recent years, rabies has been present on the island. Records in 2006 and 2007 alarmed government leaders when Bohol was listed third, then fourth, nationwide as the province with the highest rate of human deaths, posting ten deaths annually. Of the reported human rabies cases in 2007 and 2008, 25% occurred in children less than 15 years old, who had been bitten by an infected dog (6). Of the reported cases, 97% were caused by dog bites. This situation created a sense of urgency, having an alarming impact on public health and posing a possible threat to the booming industry of the province.

In 2007, a three-year Bohol Rabies Prevention and Elimination Program (BREP) was initiated by the Provincial Government of Bohol, adopting inter-sectoral programme implementation. The programme integrated expertise and resources from the sectors of agriculture, public health and safety, education, environment, legal affairs, interior and local government.

This article focuses on how the BRREP was developed and implemented over a three-year period between 2007 and 2010 in Bohol, the Philippines, and discusses specific inter-sectoral strategies for establishing sustainable rabies control and prevention programmes in resource-poor countries.

**Methodology**

The project was implemented province-wide (Fig. 1). A combination of strategies was employed to execute the sustainable canine rabies prevention and elimination programme.

![Fig. 1 Map of the province of Bohol, in the Philippines](image-url)
Legitimisation of the programme

The legal framework for implementing a rabies prevention and control programme in the Philippines was already in place at the inauguration of the BRPEP and included two National Regulations; the Republic Act No. 8485 (Animal Welfare Act) and the Philippines Republic Act No. 9482 (Anti-Rabies Act) which were enacted in 1998 and 2007, respectively (8, 9). At the local level, the provincial Governor promulgated the Provincial Ordinance No. 2007-012. The local legislation stipulated the creation of programme-implementing councils, defining their roles and responsibilities. It also described other specific components of the programme, including a penal clause.

Institutionalisation of programme-implementing councils

The BRPEP was managed by the Bohol Rabies Prevention and Elimination Council (BRPEC) under the jurisdiction of the Governor of Bohol. Canine rabies prevention and elimination were coordinated by the Provincial Veterinarian (Fig. 2). The BRPEC administered the programme's overall implementation, formulating proposals, measures and strategies that would ensure the implementation and sustainability of the BRPEP. This body also recommended the enactment of supporting legislation, policies and directives to strengthen the programme and provided timely reports to partners and the general public (5).

Parallel organisations to the BRPEP were created at the municipal and barangay level as local government units (LGU); namely, the Municipal Rabies Prevention and Elimination Council (MRPEC) and the Bantay Rabies sa Barangay (BRB) or the ‘Rabies Watchers’. The MRPEC assumed the same roles and functions as the BRB in their areas of jurisdiction, in accordance with the BRPEP. The BRB ensured the implementation of the programme at the community level, arranged mass vaccination campaigns in its areas and compiled a census of dogs and dog owners (7).

Massive programme advocacy at the community and school level

A two-pronged communication plan, including a community-focused programme and a school-based education programme, was launched at the onset of the project. Components of the information and education campaigns included discussions on rabies as a disease, its epidemiology, and its prevention and control, the BRPEP in general, responsible pet ownership and related national and local policies supporting the programme.

The community programme concentrated on campaigns using tri-media (television, radio and newspapers), displays of posters and banners in strategic areas, the distribution of flyers and other materials, public hearings of local ordinances and hosting of municipal and barangay symposia, meetings and seminars.

Philippine National Rabies Awareness Month in March and World Rabies Day, held annually on 28 September, were both observed to remind people of the continual threat of rabies and the importance of the programme to eliminate rabies on Bohol.

The school-based educational programme was developed and implemented in close collaboration with the Department of Education and in coordination with the Department of Health and other member agencies of the BRPEC. In 2009, the programme was integrated into the curriculum of all public elementary schools in Bohol, in five subjects. Other educational activities for the children included: the creation of ‘Rabies Scouts’ (boy and girl scouts who had successfully completed a rabies and responsible pet ownership training programme) and the creation of a campaign slogan to encourage responsible pet ownership.
At first, dog population data in Bohol were estimated from the 2006 census, published by the Bureau of Agricultural Statistics. Between 2007 and 2008, the BRB conducted a house-to-house enquiry to collect a barangay master list of dog owners and dogs for the province; recording the owner’s name, the number of dogs owned, the sex of the dog, whether they were confined, leashed or free-roaming. These dog population data were then updated annually.
Massive dog registration and vaccination campaign

A parenteral mass dog vaccination programme was initiated in August of 2007, with the Governor of Bohol proclaiming August 2007 as the synchronised rabies vaccination month. Only registered dogs aged three months and older were entitled to free vaccination, free dog tags and a registration card. The dog tag was valid for one year from the date of vaccination, replaceable annually upon renewal of registration, at which time a booster rabies vaccination was administered. Vaccination teams were organised at the provincial and municipal levels. Provincial teams were assigned to oversee vaccination activities and to ensure the presence and use of cold-chain equipment in every municipality. The Municipal Agricultural Officers (MAO) led the municipal vaccination teams, composed of livestock technicians, barangay livestock aides and other personnel duly designated by the MRPEC and trained as dog vaccinators. These vaccination activities were supervised by the provincial and district veterinarians. The majority of the members of the vaccination team (including those who administered the vaccine, or assisted in handling and tagging animals) received pre-exposure prophylaxis. All team members were briefed on pre- and post-rabies vaccination activities and provided with vaccination supplies and paraphernalia, as well as the necessary forms and education campaign materials.

‘Mop-up’ dog vaccination campaigns targeting low-coverage areas were conducted within six months of the initial mass vaccination. Dogs not vaccinated during the scheduled synchronised mass rabies vaccination campaigns were accommodated upon special arrangement with the municipal vaccination teams.

Standardised dog vaccination report forms were consolidated and submitted to the BRB, the MAO and the BRPEP. The community were also encouraged to bring their cats along for vaccination during the mass vaccination campaign.

Dog population management and movement control

Dog population and movement controls were implemented as part of the BRPEP and in compliance with the Anti-Rabies Act and the Animal Welfare Act. The dog population was managed by selective elimination of captured stray dogs (defined by law as any dog leaving its owner's place or premises and that is no longer in the effective control of the owner), impounded dogs unclaimed within three days, and unmanageable dogs voluntarily surrendered by owners.

Municipal rabies ordinances in the province included a section on dog population management and designated a task force to perform this function. At the barangay level, socially acceptable procedures were discussed and widely disseminated throughout the community. Euthanasia procedures were initially conducted in accordance with Administrative Order No. 21 of the Department of Agriculture on the Code of Conduct in the Euthanasia for Pets/Companion Animals. However, some owners took it upon themselves to manage their dogs. During the third year of the programme (2010), the purchase of a mobile veterinary clinic was funded by one of the partners and provided the opportunity to improve neutering, spaying, and euthanasia procedures. Additionally, partnerships were established with animal welfare organisations to improve dog population management practices to comply with the recommended international standards. Training in humane dog handling and/or catching was provided to areas with dog pounds/cages.

To further regulate the possession of dogs, establ ish dog ownership, and facilitate the traceability of dogs involved in bite cases, the mandatory registration of dogs, with a corresponding collection of fees, was implemented at the barangay level, in accordance with the Provincial Ordinance.
Registered dogs were recorded in a dog registry book. These dog registry books were distributed in every purok of the 1,109 barangays of the province. Members of BRB facilitated the entry and updating of data in this book.

Dogs from households that were not able to afford the fees were also registered and the dog owners signed a promissory note, allowing them to make a staggered payment. The collected registration fees were shared in a manner specified in the Provincial Ordinance as follows: 50% was retained by the barangay and 50% divided between the municipal and provincial treasury to support the sustainability of the entire rabies control programme.

**Capacitating and empowering various programme stakeholders**

To mobilise the various task forces, programme orientations and briefings were conducted at the municipal and barangay levels. Paralegal training was conducted by legal partners to orient programme stakeholders about the law and ordinances backing up the programme and how to use them. Programme handbooks (2), as well as reporting forms, were developed and distributed to every MRPEC and BRB to ensure uniformity in implementing the programme at all levels. These handbooks were reproduced in English and Visayan versions for easy understanding (2). Specialised training was also conducted for the technical staff of the veterinary, agricultural and health offices, including: proper dog-handling procedures, spay and neuter (vets only), animal bite management and the direct rapid immunohistochemistry test (3).

**Surveillance**

A surveillance system was established for canine rabies cases in order to ensure immediate and reliable transfer of information and follow-up, in the case of animal exposure to a confirmed rabid animal. When possible, animals involved in biting incidents were observed for 14 days. If the animal demonstrated clinical signs of rabies during the observation period, including behavioural changes or illness, it was euthanased and submitted for testing to the Regional Animal Disease Diagnostic Laboratory, located in the city of Cebu on the adjacent island province. Submitted specimens were analysed using the direct fluorescent antibody test. Laboratory results were available within one to two days and were relayed to the OPV and the MRPEC. Results were then relayed to the victims or immediate relatives through the MRPEC. The Department of Agriculture provided the sample testing free of charge but the cost of transporting specimens was assumed by the BRPEP.

**Monitoring and evaluation**

To assess the attainment of programme goals and objectives, and for planning purposes, a community-based household survey was conducted on the knowledge, attitudes and practices (KAP) of the Boholanos towards the rabies programme. The data generated also included an estimate of dog vaccination coverage, data on the owned dog population and data on the dog-human relationship. The survey was designed using questionnaires and cluster sampling procedures (1, 4).

**Results**

**Reduction in incidence of human and animal rabies deaths**

After the initiation of the campaign, a dramatic reduction in human and canine rabies cases of 50% was achieved in the year 2008. The rate of human deaths declined from ten to five, and there
were no confirmed cases of rabies in either humans or dogs (Fig. 3). Between 2009 and 2010, there were no confirmed reported human and canine rabies cases, and only one suspected human case in November 2010.

**Increased community awareness**

The 2009 KAP survey revealed that 94% of households had heard about rabies; 82.28% had knowledge of the local rabies eradication programme, 61% knew how rabies was transmitted and 85% of households were aware of the ordinances.

A total of 182,000 children or 16% of the total provincial population learned about the rabies prevention programme and responsible pet ownership through the school-based education programme.

**Increased community participation in the programme**

The successful involvement of the local communities resulted in a significant increase of community participation, from 124 purely government workers to more than 15,000, including participating local officials, volunteers and schoolteachers.

**Increased dog vaccination turnout**

Vaccination coverage of the dog population increased from 3% in 2006 to 44% between 2007 and 2008. Remarkably, it increased to 70% in 2009, despite the mandatory collection of registration fees.

**Institutionalised strategies for sustainability**

Sustainability was ensured through BRPEP activities on advocacy, general public awareness, child education, legislation and dog registration with fees (100% of which was re-invested back into the
BRPEP to establish a self-sustaining funding stream for the programme). Sustainability was strategically built into the programme through intense liaison with LGU officials, community leaders and other stakeholders to ensure community participation; the establishment of a rabies diagnostic laboratory on the island for improving disease surveillance; and the provision of an annual award system to motivate excellence in the implementation of the programme.

**Strong programme alliances resulting in fund leveraging**

The programme has generated funds from both private and public partnerships. A total of 60.5% of the funds were provided by the provincial, municipal and barangay LGUs and the community, while 39.5% were contributed by external partners.

**Institutionalised strategies for sustainability**

The following strategies were institutionalised for programme sustainability: community engagement and shared programme ownership; a deliberate campaign promoting responsible pet ownership by integrating the topic of rabies into the elementary school curriculum; disease diagnosis and surveillance to prevent the reintroduction of rabies; the adoption of a paralegal system to implement the National Rabies Law; the generation of an internal roll-over fund from the dog registry system, with registration fees collected from 95,167 dogs between 2007 and 2009; and the designation of 7,763 local Rabies Watchers in all villages of the province.

**Conclusions and recommendations**

The three-year BRPEP, initially launched in 2007, successfully achieved the goal of establishing a sustainable programme to eliminate canine rabies throughout the province of Bohol. From the early planning stages of the BRPEP, all stakeholders and partners committed themselves to building an inter-sectoral rabies control programme that would be self-sustaining when outside funding channels were no longer available. To ensure that the implementing councils could act effectively, all the members were provided with the necessary training to ensure synchronised action from the provincial level down to the barangay level.

The BRPEP was strongly supported by existing national and local laws. However, these laws needed to be understood and properly implemented if the programme was to be effective. It was understood that a sustainable and effective field operation can only be achieved when the whole community accepts and takes ownership of the programme. Thus, a massive social mobilisation, increased awareness across all levels of society and improved citizen involvement in rabies prevention activities were all major factors in creating a successful community-based rabies control and prevention programme.

In any large rabies control programme, high operational costs become significant challenges, not only for the provincial government but also for each community partner. The increased number of volunteers helped to defray the cost of the programme and improved community involvement. Volunteers are generally well known and respected by their neighbours, have a thorough knowledge of the local setting, particularly in remote areas, and are motivated to serve their own communities.

Considering the geographical situation of the island, the risk of reintroduction once the disease has been eliminated is a major challenge. Thus, strengthening rabies surveillance and monitoring down to the barangay level is vital to ensure early warning and reporting of the disease.
Acknowledgements

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References

Evaluation of various rabies elimination strategies in Latvia

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Summary

Rabies has been endemic in Latvia since the 19th Century, with fox-mediated rabies having been the main problem for the past two decades. Between 1991 and 2010, there were a total of 5,900 rabies cases in a variety of animal species, 78% of which were in wildlife, and three of which were human rabies cases. Annual prophylactic vaccination of dogs and cats against rabies is compulsory. Rabies has also been a serious problem in the countries that neighbour Latvia; namely, Lithuania, Estonia, the Russian Federation and Belarus. An epidemiological assessment revealed that two out of three oral rabies vaccination (ORV) strategies in foxes and raccoon dogs applied in Latvia between 1991 and 2010 did not have a significant effect on the rabies incidence. Because wildlife rabies was endemic throughout the country, ‘patchwork’ and small-scale vaccination (ORV strategies A and B) were ineffective and did not result in a substantial decrease in rabies incidence. Despite an increase in the number of vaccine baits used in strategy B, the rabies incidence in the following years actually increased. Only large-scale vaccination covering the entire country (ORV strategy C) resulted in a drastic decrease in rabies incidence within a short period of time. Hence, this large-scale and long-term ORV strategy will take less time to eliminate rabies, as has been shown in several other European countries, provided international recommendations are followed. Although implementation of large-scale vaccination requires a large amount of financing and strict organisation at the beginning, in the end it is more cost-effective than any other strategy.

Keywords


Introduction

Rabies is life-threatening for humans and the most important viral zoonosis from a global perspective (3). The main rabies virus reservoirs in the Baltic States are red foxes (Vulpes vulpes). Though it has not yet been proven, there is an indication that the raccoon dog (Nyctereutes procyonoides) may represent a second reservoir species (7, 12, 13). The first written evidence of rabies cases in Latvia dates back to 1822. Rabies has been endemic in Latvia since the 19th Century. Before 1951, most of the cases were recorded in dogs, but later cases in wildlife, namely red foxes (Vulpes vulpes) and
wolves (*Canis lupus*), were diagnosed annually. The first case in a raccoon dog (*Nyctereutes procyonoides*) was reported in 1958. By 1963 the disease had become mainly sylvatic (14), with fox-mediated rabies having been the main problem for the past few decades. Between 1991 and 2010, a total of 5,900 rabies cases were diagnosed in a variety of animal species, of which 78% were wildlife. Three human rabies cases also occurred. Initial rabies control attempts targeted domestic animals and prophylactic vaccination against rabies became compulsory for dogs in Latvia in 1977, and for cats in 1991 (14). The first oral rabies vaccination (ORV) field trials in Latvia were conducted in 1991 (11) and, since that time, various ORV strategies have been applied. The aim of this study is to evaluate the impact of these ORV strategies on the rabies incidence in red foxes and raccoon dogs in Latvia, between 1991 and 2010.

**Materials and methods**

The Republic of Latvia comprises an area of 64,589 km². Forests cover 44% of the country, offering excellent habitats for wildlife. Latvia is situated on the coast of the Baltic Sea and has borders with Lithuania, Estonia, the Russian Federation and Belarus. Between 1991 and 2010, depending on the availability of financial resources, the Food and Veterinary Service applied three different ORV strategies, which can be characterised as follows:

a) patchwork vaccination (1991 to 1997), referred to as **strategy A**. During this time period, about 28,000 vaccine baits were manually distributed, with an average bait density of 4 baits/km², but only in those regions with the highest rabies incidence. At the time, chicken heads were used as baits for the vaccine. The vaccine was produced in the Russian Federation and did not contain a biomarker. ORV campaigns were organised by the State Veterinary Service, in collaboration with the Hunters’ Association. During the vaccination campaigns, vaccine baits were placed near the fox dens. The ORV campaigns during this period were not carried out regularly and, due to the vaccine type used, it was impossible to monitor bait uptake in the target animals;

b) small-scale vaccination (1998 to 2004), referred to as **strategy B**. Manufactured vaccine baits (*n* = 1,106,100), containing tetracycline as a biomarker, were manually distributed, with an average bait density of about 11 baits/km², in discrete regions of the country. The distribution of the vaccine baits was organised in a similar way to the distribution in strategy A; however, the number of vaccine baits and the size of the vaccination area were considerably increased. Monitoring the ORV campaigns focused on the determination of bait uptake only, as serological methods were not in use at that time;

c) large-scale vaccination (2005 to 2010), referred to as **strategy C**. During this period, the entire territory of Latvia was covered with manufactured baits (*n* = 15,219,200), using aerial distribution, with an average bait density of 24.1 baits/km². Monitoring the ORV campaigns included determination of bait uptake and herd immunity in hunted target animals.

The details of the ORV campaigns carried out in Latvia from 1991 to 2010 are given in Table I.

The efficacy of the three ORV strategies (A, B and C) in reducing the incidence of rabies in the country was analysed and compared. The analysis of variance (ANOVA) single factor test was used to compare rabies incidences, after the application of three ORV strategies, and during the years in which strategy C was carried out.
Table I
Details of the different oral rabies vaccination campaigns carried out in Latvia from 1991 to 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of ORV campaigns</th>
<th>No. of regions vaccinated</th>
<th>Vaccinated area (km²)</th>
<th>No. of baits distributed</th>
<th>Average bait density (baits/km²)</th>
<th>Vaccine virus strain used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>1</td>
<td>1</td>
<td>403</td>
<td>333</td>
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<tr>
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<td>1</td>
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<td>3,000</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
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<td>2</td>
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<td>2</td>
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<td>12,000</td>
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<td>6.6</td>
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<td>2</td>
<td>26</td>
<td>32,000</td>
<td>310,000</td>
<td>9.7</td>
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</tr>
<tr>
<td>2002</td>
<td>2</td>
<td>26</td>
<td>24,000</td>
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<tr>
<td>2003</td>
<td>2</td>
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<td>300,000</td>
<td>12.5</td>
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<td>2004</td>
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<td>–</td>
<td>–</td>
<td>–</td>
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<td>2005</td>
<td>2</td>
<td>15</td>
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<td>2</td>
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<td>2007</td>
<td>2</td>
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<td>3,200,000</td>
<td>24.7</td>
<td>SAD B19</td>
</tr>
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</table>

ORV: oral rabies vaccination

Results

An epidemiological analysis revealed that ORV strategies A and B, applied between 1991 and 2004, did not have a significant effect on the incidence of rabies. Whilst the rabies incidence remained relatively unchanged between 1991 and 1997, the situation worsened in the following years. Moreover, despite ORV campaigns carried out twice a year, and an increase in the size of the vaccination area and vaccine bait density to 11 baits/km² in strategy B, the number of rabies cases reported from all over the country drastically increased, resulting in a peak in 2003 (963 cases; 86% of which were in wildlife species) (Fig. 1). Owing to the increase of rabies incidence, a statistically significant difference ($p < 0.05$) was detected between rabies incidences during the application of ORV strategies A and B.

Only a change to strategy C, using aerial distribution of baits and a recommended standard average bait density, was effective. After the second year (2006), when ORV strategy C had been implemented throughout the whole territory of Latvia, the rabies incidence significantly decreased ($p < 0.05$), except for the year 2009. In total, during the five years after the implementation of large-scale aerial distribution of vaccine baits in Latvia, the rabies incidence decreased from 421 cases in 2005 to 16 cases in 2010 (Fig. 1).
The reasons for the failure of ORV strategies A and B are likely to be very low vaccine bait density and selection of an insufficiently large vaccination area. Because strategy A focused exclusively on the infrequent conducting of ORV campaigns in areas with a high number of rabies cases, this approach resulted in a patchy spatio-temporal pattern of vaccination areas to no avail and so cannot really be called a vaccination strategy at all. It was, rather, a ‘Latvian’ proof of principles under field conditions. The minimum size of a vaccination area should be 5,000 km² at least (4). However, whenever possible and feasible, the size of the vaccination area needs ideally to include the entire infected area, or be as large as possible, and extend up to natural or artificial barriers (4). Therefore, it remains a matter of speculation whether the vaccine virus strain used from 1991 to 1996 also contributed to the failure of ORV strategy A. Even the implementation of large-scale ORV campaigns twice a year in 1998 – after a year of interruption of ORV activities – using an altered mode of bait distribution and an adapted bait density did not have the desired effect. In fact, vaccination strategy B was obviously a half-hearted approach too, as it did not consider the basic principles and recommendations of ORV programmes, especially in terms of vaccine bait density and monitoring ORV campaigns (4). Based on field experience gained from vaccination campaigns in various countries and computer simulation models, densities of 18 to 20 and 20 to 30 baits per km² are advisable for low and high fox population densities, respectively. There is evidence that budget constraints led the Latvian veterinary authorities to use a still unfavourable bait density and mode of bait distribution at the time. These facts, and the increasing infection pressure from unvaccinated areas and neighbouring countries, might explain the drastic increase of the number of rabies cases in Latvia between 1998 and 2003. This is supported by:

Fig. 1
Development of rabies cases during the implementation of the various oral rabies vaccination strategies in Latvia
Arrows indicate the number of oral rabies vaccination campaigns conducted in the respective years

Discussion
the fact that ORV was not carried out in neighbouring Lithuania from 2001 to 2004, resulting in a drastic increase in rabies incidence in the following two years (16), which is the highest rabies incidence recorded in the Baltic States to date. At the same time, the number of rabies cases increased in Estonia too, resulting in a peak in 2003 (10).

Unfortunately, strategies A and B were ineffective from both an epidemiological and economic point of view, as the direct and indirect money spent on those ORV campaigns was lost. So far, in Latvia, only strategy C has complied with the basic recommendations and requirements for ORV programmes as stipulated by the European Commission (EC) (4).

Rabies has also been endemic in countries neighbouring Latvia, e.g. Lithuania, Estonia, the Russian Federation and Belarus, where the disease has been present for the last few decades. Lithuania has had similar experiences with inappropriate ORV strategies. Here, ORV was implemented through the Lithuanian National Rabies Prevention Programme during the period of 1995 to 2000 (7). Approximately 920,000 vaccine baits were distributed manually across an area of more than 8,000 km² in 27 of the 44 districts of Lithuania, using a vaccine bait density of 15 to 25 baits/km² (8). As in Latvia, this strategy did not produce favourable results as the rabies incidence in red foxes and raccoon dogs increased significantly (15), confirming that manual distribution of baits, even at higher densities, is ineffective. Only the implementation of a large-scale ORV campaign in the spring of 2006, two years after the cessation of an earlier ORV programme due to lack of financial resources, in an area of more than 40,000 km² in the south-eastern and central parts of Lithuania and subsequently covering the whole country, using aerial distribution, resulted in a similar decrease in rabies incidence in Lithuania (17). In contrast, in Estonia, after initial ORV field trials had been carried out on Vromsi Island in 2004 (9), a well-planned and strategically designed large-scale ORV programme was implemented in autumn 2005. Within four years, this campaign resulted in a drastic decrease of rabies incidence and an almost virtual elimination of rabies in the country (6, 10). There is limited information available about rabies control measures in the Russian Federation and Belarus. ORV campaigns, co-financed by the EC, are carried out in the Kaliningrad region and near the border with Finland (5, 6). Rabies is also endemic in Belarus with some sporadic human cases every year. ORV campaigns have been implemented in certain areas, and a slight rabies incidence decrease has been observed during the last few years (5).

Conclusions

Numerous European countries are free of rabies in terrestrial animals, either because they were never affected by wildlife rabies; for example, Ireland, the United Kingdom, Sweden, Norway, Denmark, Spain and Portugal, or due to successful ORV campaigns; for example, Finland, the Netherlands, Luxembourg, Belgium, France, Switzerland and the Czech Republic (2). In 2008, Germany and Austria were the last European countries to join the list of rabies-free countries, whilst wildlife rabies still predominates in the Baltic States (1). These countries are expected to eliminate rabies from their territories in the near future, provided that existing World Organisation for Animal Health (OIE), World Health Organization (WHO) and European Union (EU) recommendations on ORV are strictly followed, ORV is continued in neighbouring countries and cross-border activities are coordinated.

Recommendations

To avoid unnecessary expenditure on rabies control, small countries should avoid ‘patchwork’ and small-scale vaccination but consider strict implementation of a large-scale and long-term ORV programme covering the entire country to control wildlife-mediated rabies. Sufficient long-term funding is of the utmost importance in achieving freedom from rabies within a short period of time.
To be cost effective and to eliminate rabies within the minimum time, it is essential to follow OIE, WHO and EU recommendations on ORV.

As rabies in wildlife reservoirs is a global problem, collaboration between neighbouring countries is very important during the process of planning and implementing a common large-scale ORV programme. The OIE should be pivotal in facilitating these collaborations, especially in regions where rabies is endemic.

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References


RECOMMENDATIONS

of the OIE Global Conference on Rabies Control

7–9 September 2011

Incheon-Seoul, Republic of Korea
Recommendations

CONSIDERING THAT:

1. Rabies is a widespread, neglected and under-reported zoonosis with an almost 100% case fatality rate in human and animal untreated on time, and causing a significant social and economic burden in many countries worldwide;

2. On a global level, the main reservoir of rabies is the dog, responsible for almost 99% of fatal rabies cases in humans;

3. Only 32 out of the 178 OIE Member Countries would be eligible to qualify for historical freedom in accordance with the provisions of the *Terrestrial Code* or have successfully eliminated rabies in domestic animals, while at least 110 Member Countries are considered endemically infected with rabies; only in 161 Member Countries is rabies a notifiable disease in dogs;

4. Good veterinary governance is a prerequisite for compliance with international standards, guidelines and recommendations for rabies prevention and control in animals;

5. In spite of the availability of scientific methods to control rabies in dogs the effective implementation of such rabies control programmes and technologies are dependent on political will, community commitment and sufficient financial resources at the global, regional, national and local levels;

6. The control and elimination of rabies in dogs, through vaccination remains the only cost-effective way to sustainably protect humans from contracting the disease;

7. Massive culling of dog populations or wildlife, as isolated, interim or emergency control measures, is neither sustainable nor scientifically supported for efficiently controlling or eliminating dog-mediated rabies;

8. On-going assessment of the global burden of rabies will help to better advocate for rabies control worldwide;

9. The OIE, WHO and FAO have published a concept note on the sharing of responsibilities and coordinating their global activities to address health risks at the animal-human-ecosystem interfaces;

10. Rabies in wildlife reservoirs remains important in many parts of the world and endangers biodiversity particularly where wildlife become victims of dog-mediated rabies;

11. The OIE has adopted and continually updates international standards related to rabies prevention and control;

12. The regular training of OIE National Focal Points for Animal Disease Notification and for Wildlife have increased their knowledge of and reporting on the rabies situation in their respective countries;

13. The OIE twinning initiative is improving the capability and access of Member Countries to rabies diagnosis and scientific expertise in some regions of the world;

14. OIE Reference Laboratories and WHO Collaborating Centres on rabies have considerably contributed to the development of safer, more effective rabies vaccines and other rabies biologicals, diagnostics test and preventive and control methods;
15. The OIE is promoting and implementing the concept of regional vaccine banks for dog vaccination;

16. An increasing number of non-governmental organisations are supporting rabies control at the animal source and rabies awareness campaigns;

17. The goal of this conference was to support global rabies elimination while providing a global platform to encourage exchanges of experiences on rabies prevention and control at the animal source and to seek for renewed concepts of inter-sectoral collaboration between stake-holders.

RECOMMENDS THAT:

1. Governments, donors, foundations and NGOs be mobilised at global level with the guidance of the OIE, WHO and FAO to continue to invest in dog rabies prevention and control and to increase and sustain the momentum of the global control and subsequent elimination of rabies with emphasis on dog rabies;

2. All governments consider rabies control as a high priority and ensure that national legislation provides for rabies to be a notifiable disease;

3. The OIE, WHO and FAO should consider rabies a priority and should encourage international solidarity and donor support for countries in need of funding to initiate and sustain control programmes for rabies;

4. OIE Member Countries are encouraged to support awareness campaigns on rabies (e.g. participate in the World Rabies Day initiative);

5. The re-assessment of the global burden of rabies (in animals and humans) and the assessment of cost-effectiveness be completed to provide updated data to better advocate for rabies control at the global level;

6. The governance of Veterinary Services be strengthened through the active participation of countries in the PVS pathway of the OIE to enhance their capacity and ability and make appropriate financial and human investments to control rabies;

7. Veterinary services of endemic countries in collaboration with the public health services (Ministry of Public Health), municipalities and local communities mobilise appropriate financial support from the public budget and other sources to benefit from the cost-effective advantage of eliminating rabies at the animal source;

8. The budget for rabies control programmes should include the cost and accessibility of human vaccines to protect veterinarians, para-veterinarians, laboratory staff and other personnel directly involved in rabies control programmes to mitigate any professional hazard leading to rabies infection;

9. Options for combining rabies control programmes with other interventions or zoonosis prevention and control programmes should be actively considered;

10. Surveillance and reporting of rabies, in humans, domestic animals and wildlife, be continually improved nationally and globally, and the data so generated should be shared across sectors through e.g. WAHIS/WAHID and GLEWS;

11. Definitive diagnosis of rabies in animals should only be confirmed by laboratory tests as described in the OIE Terrestrial Manual;

12. OIE Reference Laboratories and WHO Collaborating Centres continue their work on international harmonisation of laboratory methods for the diagnosis and the quality control of vaccines as well as development/evaluation of new techniques and methodologies for rabies control;
13. Laboratory twinning / training programmes should be encouraged to further improve diagnostic capability in laboratories in developing countries;

14. Strategic implementation and continuous evaluation of control programmes throughout the world should be undertaken to enhance and improve the decision-making ability for the most appropriate vaccination strategies;

15. Control strategies be continuously reviewed and adapted taking into account, e.g. dog population density, population turn-over and accessibility;

16. More research on practical and feasible chemical or immuno-contraception with the possibility for use in combination with parenteral or oral rabies vaccines should be supported, with due consideration to safety, public and animal health and ecological aspects of oral vaccines;

17. OIE standards on rabies prevention and control should be continuously updated to reflect new scientific advances;

18. The OIE extend the establishment of regional vaccine banks to provide access to high quality vaccines to countries in urgent need;

19. Dog population management be applied in compliance with OIE standards;

20. Public awareness and education on rabies be a national priority and be enhanced by exchange of information, experience and cooperation between medical, veterinary, educational, environmental and customs authorities, relevant communication channels and the private sector;

21. Governmental and non-governmental organisations active in rabies control should communicate and coordinate their technical and financial efforts with national authorities and international organisations, to maximise sustainability of their collaboration and joint projects;

22. The OIE, WHO and FAO continue to encourage governments to update their legislation to comply with relevant standards for efficient rabies prevention and a ‘One Health’ approach to disease control;

23. Dog population management, rabies control and animal welfare be included in the basic core curriculum of the initial training of veterinarians and para-veterinarians;

24. Veterinary Statutory Bodies should ensure that their rules provide for the ethical conduct required from veterinarians and para-veterinary professionals in situations where rabies poses risks to animals and humans;

25. Rabies control be considered as a global public good eligible to international solidarity and donors support where needed, as well as a priority model to apply the ‘One Health’ concept by countries and intergovernmental organisations.