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EPIDEMIOLOGY AND ELIMINATION OF RABIES IN WESTERN EUROPE

P. P. Pastoret and B. Brochier

Department of Immunology-Vaccinology, Faculty of Veterinary Medicine, University of Liège, 20. boulevard de Colonster, B-4000 Liège, and "'Rabies Unit, Pasteur Institute o/ Brussels, 642. rue Engeland. B-1180 Brussels, Belgium

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ABSTRACT

In recent years, most of the research on the control of sylvatic rabies has concentrated on developing methods of oral vaccination of wild rabies vectors. In order to improve both the safety and the stability of the vaccine used, a recombinant vaccinia virus, which expresses the immunizing glycoprotein of rabies virus (VRG), has been developed and extensively tested in the laboratory as well as in the field. Between 1989 and 1995, several million VRG vaccine doses have been dispersed in Western Europe for the vaccination of red foxes, leading to the elimination of sylvatic rabies from large areas, which have consequently been freed from the need for vaccination. This approach ma)' have consequences for the regulation of pet movement within the whole European Union.

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INTRODUCTION

The present Western European terrestrial epizootic of rabies has spread some 1400km westwards from Poland since 1939. For several years, the front of the epizootic advanced 20-60km per year (Toma & Andral, 1977; MacDonald, 1988). This terrestrial epizootic is sylvatic: the reservoir of infection is in wildlife. While all susceptible species, both wild and domestic can develop rabies, the red fox (*Vulpes vulpes*) is involved in more than 75% of cases and is both the vector of the disease and its reservoir. Although the red fox plays a key role in the maintenance of the disease, it does not usually transmit it directly to humans which are mainly at risk from affected domestic animals such as cattle (Pastoret *et al.,* 1995). The dog is, however, a rare excretor of the vulpine strain of rabies.

The percentage of rabid foxes is underestimated for several reasons. In fact, the proportion of rabies cases reported is likely to be as low as 2-10%; this can cause problems in detecting outbreaks (Bacon, 1981) and, conversely, the impact of the epizootic on wildlife is therefore important (King & Turner, 1993). For example, the occurrence of the disease in cubs in the den is always neglected, but could be frequent (Thiriart *et al.*, 1985). The fox seems to be the only species maintaining the present terrestrial epizootic; if rabies were to be eliminated from the fox population it would cease to be a problem in other wildlife or domestic species. In Western Europe, rabies is considered a source of economic loss and, above all, hampers the movement of animals between the different member states of the European Union (EU). This has serious implications for the 'open market' since some member states are currently rabies free and wish to maintain their disease-free status. Therefore, the control of rabies requires a common strategy to be established at EU level.

In 1986, several infected EU countries decided to tackle this task together (Pastoret *et al.*, 1987; Brochier *et al.,* 1988) by vaccinating foxes orally against rabies. This programme was supported by the European Gommission from the beginning and has led to the near extinction of fox rabies in Western Europe. Thus, the situation is rapidly evolving in the field, and it is timely to consider modifying EU rabies regulations.

HISTORY OF URBAN RABIES IN GREAT BRITAIN

Rabies may be maintained in two not necessarily interrelated cycles, urban and sylvalic. Urban rabies, affecting stray and feral dogs and cats, is by far the more dangerous to humans, accounting for an estimated 99% of all recorded human cases and for 92% of all human post-exposure treatments (Pastoret *et al.*, 1995). Sylvalic rabies is characterized by the involvement of one or two main species in particular locations and this pattern remains stable over many years (Chalmers & Scott, 1969). In continental Europe, sylvalic rabies has been reported since the Middle Ages but has

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been intensively studied only since the current upsurge began at the beginning of World War II (King & Turner, 1993) when urban rabies had virtually disappeared.

Rabies was a common disease in Cheat Britain for many centuries (Fleming, 1872; King & Turner, 1993). The first allusion to the disease seems to have been in 1026 in the laws of Howell the Good of Wales (cited by Fleming, 1871). The prevalence of the disease increased from 1735, and by 1776 rabies was widespread in dogs throughout Britain. Mad dogs were reported in London from 1752 to 1862. Despite a significant fox population, the disease was not observed in wildlife except for two outbreaks in deer at Barnsley in 1856 when 100 animals were affected, and in Richmond Park, London, in 1886, when 257 fallow deer (*Cennts dama*) died but did not pass on the disease to red deer (*Omits elafihus*) in the same park.

Between 1889 and 1898, over 160 human cases of rabies were recorded in Britain. From 1897 onwards, the implementation of Orders, which included powers for the muzzling of dogs, the elimination of stray dogs, the tracing of movement of rabid dogs and their contacts, and the regulation and control of the importation of dogs, led to the eradication of the disease for the first time in 1902. Rabies was reintroduced in 1918 and 328 further animal cases were found in the south of England before the disease was finally eradicated in 1922. However, since then, a further 21 recorded human deaths have resulted from infection acquired abroad. Except for two dogs, which became rabid after release from quarantine, import regulations, including quarantine of imported dogs and cats, have kept Britain free of animal rabies since 1922.

During the 49 year period 1922-1970, 29 animals have died of rabies in quarantine. However, in the 21 year period (1971-1991) since the immunization of cats and dogs with inactivated vaccines of cell culture origin within quarantine was introduced, only two dogs have died in quarantine with evidence of rabies in the brain. Since 1971, of nearly 200000 imported cals and dogs immunized within quarantine, none has died of rabies after release. It should also be noted that among all the cases of rabies in animals imported into Britain, none was due to a previous contamination with fox rabies in another country belonging to the EU. In fact, urban rabies disappeared from other western European countries during the same period.

BIOLOGY OF RABIES VIRUS INFECTION IN FOXES

The present epizootic of fox rabies in Western Europe seems to have started at the Russian-Polish border, and the prevailing hypothesis is that the virus originated in dogs and became adapted, through successive stages, for foxes (Winkler, 1975). The virus strain is highlv pathogenic for the fox: a dose of 0.3 mouse intracerebral LD_{30} is sufficient to kill one fox in Iwo, whereas domestic carnivores require a dose 1000000 times greater to produce the same effect (Blancou *et al.*, 1991a). As the rabies front penetrates a new area, the foxes within the area suf fer an epizootic of the disease and when the fox population has been severelv reduced, the incidence of the disease decreases and remains low for a 'silent' period of some 2-3 years. After the initial epizootic, secondary enzootic outbreaks recur, often at intervals of 3-5 years (Macdonald & Voigt, 1985).

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Superimposed upon the annual variance in the incidence of reported cases of vulpine rabies is a seasonal pattern. Cases tend to peak in late winter and reach a trough in midsummer. The late winler/early spring peak seems to be linked to the mating season of foxes. In recent years, the advance of the rabies epizootic, which had previously progressed 20-60km year in Europe, seems to have stopped, possibly due to strain variations or to the ecology' of transmission.

In Europe, the fox is certainly the animal species most susceptible to vidpine rabies infection, and the proportion of rabid foxes that excrete the virus is very high: 93-100% of rabid foxes harbours the virus in the salivary glands and excrete it in large amounts in saliva. Furthermore, the virus can be excreted for up to 29 days before the onset of the disease (Aubert *et al.*, 1991).

The incubation period of the disease in foxes depends mainly on the dose of virus with which the animal has been infected and varies from 10-41 days. The clinical disease, which is transmitted by biting, lasts 3-5 days. The signs are variable (George *et al.*, 1980), The furious form is relatively rare and most animals become apathetic and develop paralysis. Since the apathetic form of the disease predominates in the fox, rabid foxes do not usually wander far from their original territory (Artois & Aubert, 1985). This may explain why the front of a fox rabies epizootic progresses slowly.

CONTROL OF FOX RABIES

Prophylactic measures taken in the past, such as the destruction of foxes to reduce the population, did not prevent the spread of the epizootic. During recent years, most of the research on the control of fox rabies has concentrated on the development of methods of oral vaccination of the fox (Steck *et al.*, 1982) which has been extensively used in all infected countries of the EU. The research has focused on oral vaccination because it is the only means of immunizing a sufficient proportion (75%) of wild foxes, through the distribution of vaccine baits; as such, the only vaccines that could be used were either attenuated strains of rabies virus or live, vectored vaccines. Inactivated rabies vaccines are useless when given orally (Brochier et al., 1985).

In 1986, in order to develop a common strategy for the EU, a coordinated trial of oral vaccination of foxes was undertaken in several European countries using the SAD B19 attenuated strain of rabies in order to assess both the efficacy and the feasibility of the method (Pastoret et al., 1987). The results of these campaigns confirmed the efficacy of fox vaccination for the control of sylvatic rabies.

The use of attenuated rabies virus, however, remains controversial as far as safety and stability are concerned, as these virus strains are still pathogenic for laboratory, and wild rodents, as well as for wildlife species, such as the chacma baboon (*Papio ursiniis*) and target species such as the striped skunk (*Mephitis mephitis*) (Pastoret *et al.*, 1994); moreover, these strains may still be pathogenic to man. Humans exposed to SAD-derived attenuated strains of rabies must be treated with a conventional inactivated rabies vaccine which elicits good cross-protective immunity. The SAD-derived attenuated strain may also be inefficient for some rabies vectors such as the racoon (*Procyon lolor*) in North America.

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The pathogenicity of attenuated rabies virus strains can be abolished by mutating arginine residues at position 333 of the rabies virus glycoprotein (Tuffereau *et al.,* 1989). This has led to the development of a new attenuated vaccine strain already used in the field (Kihm *et al.*, 1992). Nevertheless, another inconvenience of attenuated strains of rabies virus is their heat sensitivity (Pastoret *et al.*, 1996) which reduces their potential efficacy in field conditions. In order to improve both the safety and stability of the vaccines used for fox vaccination in the field, a recombinant vaccinia virus which expresses the immunizing glycoprotein of rabies virus (VRG) has been developed and tested in the field for oral vaccination of foxes (Kieny *et al.*, 1984; Blancou *et al.,* 1986; Brochier *et al.*, 1990; Pastoret *et al.*, 1992).

DEVELOPMENT AND DELIBERATE RELEASE OF A VACCINIA-RABIES GLYCOPROTEIN RECOMBINANT VIRUS (VRG) FOR ORAL VACCINATION OF FOXES AGAINST RABIES

The recombinant vaccinia-rabies glycoprotein virus (VRG) has been tested for efficacy and safety in the fox (Blancou *et al.*, 1986; Boulanger *et al.*, 1995). The duration of protection conferred by VRG, a minimum of 12 months in cubs and 18 months in adult animals, corresponds to the length of protection required for fox vaccination in the field, due to the high turnover of the population. The efficacy of VRG contained in a machine-made baiting system has been tested (Brochier *et al.*, 1990a) and shown to be effective.

VRG was shown to be non-pathogenic in the fox (Pastoret *et al.,* 1992; Boulanger *et al.*, 1995) whatever the inoculation dose or route of administration. No transmission of immunizing amounts of VRG was found to occur in adult or young foxes, with the exception of one adult fox bitten by another fox which had been fully vaccinated. VRG only multiplies locally (Thomas *et al.*, 1990).

The influence of vaccination with VRG on the onset of the disease and on the delay before death in foxes previously infected with wild rabies virus has been investigated. The results show that 'early' and 'late' death phenomena occur as a consequence of interactions between oral vaccination with VRG and rabies infection, but preclude the risk of the emergence of asymptomatic carriers of wild-rabies virus after vaccination (Brochier *et al.*, 1989a). Field trials with baits have shown that several non-target wildlife species compete with foxes for bait consumption. It must also be recognized that, within the orthopoxvirus group, vaccinia virus has a wide range of host species. In fact, bait-uptake monitoring and tetracycline (included as a biomarker within the bait) detection controls, performed after vaccination campaigns, proved that mustelids, wild boars (*Sus scrofa*) and domestic carnivores may ingest the vaccine bait and a significant proportion of the baits are partly eaten by small mammals. It was therefore important to verify the safety of VRG for non-target species (both domestic and wild).

Several non-target wild species were chosen for testing in Europe because of their opportunistic feeding behaviour and their presence in the areas where the vaccine is to be distributed (Brochier

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et al., 1989b, 1996); these include wild boar, the Eurasian badger (*Meles meles*) and several micromammals. No clinical signs of rabies and/or pox-inflicted lesions were observed in the vaccinated animals during the observation period (28 days minimum after vaccination). Similar experiments were undertaken in the United States of America in other target species (Hanlon *et al.,* 1997); serological surveys of orthopoxvirus circulation in wild mammals were also done, showing that the risk of recombination between the recombinant vaccinia-rabies virus and a wild orthopoxvirus such as cow-pox were nearly nil (Boulanger *et al.,* 1996).

Taking into account all the available experimental data concerning the safety of the VRG for target and non-target species and its efficacy in foxes, limited field trials of fox vaccination with the recombinant virus were authorized first by the Belgian (Pastoret *et al.*, 1988; Brochier *et al.*, 1991) and then by the French public health authorities. Similar trials were also undertaken later on in the United States of America (Brochier *et al.,* 1996; Hanlon *et al.,* 1998).

TOWARDS ELIMINATION OF RABIES WITHIN THE EUROPEAN UNION

The last trial of deliberate release of the VRG on a 2200km2 area of Southern Belgium was intended to test the feasibility of rabies eradication over a large area (Brochier *et al.*, 1991). The 25 000 bails containing VRG and a tetracycline biomarker were dropped by helicopter on three occasions (November 1989, April 1990 and October 1990). After the third phase of vaccination, 81% (64/79) of inspected foxes were tetracycline positive. Only one rabid fox was recorded, at the periphery of the baited area, and this was tetracycline negative. Despite the dramatic decrease in the number of rabid foxes recorded after vaccine-bait distribution, the efficacy of the vaccination campaign remains difficult to evaluate because systematic collection of foxes is not logistically feasible. Nevertheless, because notification of cases of rabies in cattle and sheep is mandatory in Belgium, the incidence of rabies in livestock provides a reliable indicator of the prevalence of rabies in the wild. No case of livestock rabies has been recorded in the study zone since the second phase of vaccination. On this occasion. we investigated also the economics of the vaccine-baits dispersal programme. The average yearly cost of rabies in Belgium (1980-1989), including post-exposure treatments of humans, animal diagnosis, compensation to farmers for the culling of infected livestock, and the culling of wild foxes, was estimated to be 400000 ECUs per 10000 km-, or 88000 ECUs per year for the area under study. These figures did not include the cost of vaccination of domestic animals nor the salaries of civil servants. In comparison we estimate the overall expenditure during the three campaigns of vaccine-bait distribution to be 118000 ECUs. Because vaccination following elimination can, in principle, be interrupted or subsequently limited to the borders of the vaccinated zone, long-term maintenance of a rabies-free area by peripheral vaccination with VRG is economically justifiable. The use of VRG has now been extended to all the contaminated areas in Belgium and to the Grand Duchy of Luxemburg as well as to large areas in

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France. Rabies is now close to being eliminated from these three countries (Brochier *et al.,* 1996, 1997).

The elimination of rabies in Belgium has already had other beneficial effects, besides the improvement of animal health. First, the number of human post-exposure treatments has decreased in proportion to the decrease of rabies incidence in animals (mainly cattle). Second, the diminution of rabies incidence in wildlife has had a beneficial effect on the survival of threatened wild species, such as the Eurasian badger in the contaminated area, and estimates of the badger population in the treated area are now showing a gradual increase.

VACCINATION OF PETS AGAINST RABIES

Although between 1884 and 1885, Pasteur demonstrated the possibility of vaccinating dogs, it was only in the 1920s that domestic animal vaccination was developed and used in practice. The first vaccine widely used was the Semple type (Umeno & Doi, 1921). Later on, attenuated live virus and inactivated virus vaccines were developed. The adaptation of the fixed Flury strain to chicken embryos (Koprowski & Cox, 1948; Koprowski, 1954) led to the selection of two strains differing in the number of passages. Other strains, such as the ERA (Abelseth, 1964a, b), SAD, Kelevetc., have also been developed. Although only preventive vaccination of animals (before their exposure to the rabies virus) is authorized, in some instances post-exposure vaccination is possible, and curative treatments have been tested in several species.

Rabies virus can be inactivated by physical agents (heat or ultraviolet rays) or chemical agents (phenol, ether, formalin, B-propiolactone, tri-N-butyl phosphate, ethyleneamine, or carbolic acid) or combinations of the two. Many cell-culture vaccines have been produced on either primary cells or cell lines (Soulebot *et al.,* 1978; Precausta and Soulebot, 1991; Pastoret *et al.,* 1993, 1997).

One other route to produce vaccines involves the elaboration of antigenic material based upon non-replicating viral vectors expressing G protein, purified Ci protein, subfragments of G, or anti-idiotypic antibodies raised against G (Prehaud *et al.,* 1989). Other possibilities involve the use of new adjuvants (Morein *et al.*, 1984; Osterhaus *et al.*, 1986) or the addition of other rabies virus components, such as the N protein. The most promising new development comes, however, from abortively replicating avipoxvirus vectors. The natural productive host range of avipox viruses is limited to avian species. Nonetheless, abortive infection can be initiated *in vitro* in cell lines derived from non-avian species. Using avipox virus recombinants, foreign antigens can be authentically synthesized, processed and presented on the infected cell surface without infectious progeny virus being produced. Fowlpox and canarypox rabies recombinant viruses have been developed in which the gene coding for the rabies virus glycoprotein is expressed under the control of vaccinia virus promoters (Taylor *et al.*, 1988,1991).

Preventive vaccination being the rule in veterinary medicine, post-exposure vaccination can be allowed only if the animal, such as the dog, has been previously vaccinated before exposure. In such cases, failure to protect the animal has been reported in very few instances (1/3000). Some

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experiments have been conducted in dogs, cats and sheep to check whether post-exposure treatment of these species was feasible and efficient. In sheep, it was shown that post-exposure treatment with rabies immunoglobulin and tissue culture vaccines protected all animals, but some animals which were treated only with vaccine died of rabies (Blancou *et al.*, 1991b).

PRESENT RABIES CONTROL MEASURES IN THE UNITED KINGDOM

For most of this century, rabies control measures in Britain have relied on 6 months quarantine in approved premises for all mammals, except farm-stock and horses which are subject to other controls. All animals entering quarantine have been required to be vaccinated with an approved, inactivated rabies vaccine, and dogs also had to be vaccinated against distemper. Vaccination other than in quarantine or for export has not been allowed in the UK. In recent years, however, commercially traded dogs from EU States no longer had to undergo quarantine, but must come from approved premises, be vaccinated, test positive for antibody and be permanently identified with a microchip transponder (Pastoret *et al.*, 1998).

TOWARDS NEW EUROPEAN REGULATIONS

As mentioned in the introductory section of this paper, rabies in Western Europe is considered a source of public health concern, economic loss and hampers the movement of animals between the different member states of the EU. Some member states, such as the UK, Spain and Portugal, are currently rabies free and wish to maintain their disease-free status. Therefore, the control of rabies requires a common strategy established at EU level. This has already begun since the European Commission pays for half of the fox rabies elimination programme cost and the programmes are discussed between the different countries concerned before implementation.

Within the EU, a country will be declared rabies free after 2 years of epidemio-surveillance without any reported case of rabies in either wildlife or domestic animals. If previously infected member states become rabies free, it seems appropriate to consider the possibility of changing the rules governing animal traffic within the EU. The case for quarantine containment in the UK for pets coming from other rabies-free areas of the Union is particularly hard to justify bearing in mind that fox rabies has not been introduced into Spain by pets, travelling freely from contaminated countries; moreover, of the rabies cases in UK quarantine kennels, none originated from another member state of the EU. The risk of introducing fox rabies into the UK through pets from other member states is practically nil.

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