# Oral immunization against rabies : afterthoughts and foresight

Autor(en): **Wandeler, A.I.**

Objekttyp: **Article**

Zeitschrift: **Schweizer Archiv für Tierheilkunde SAT : die Fachzeitschrift für Tierärztinnen und Tierärzte = Archives Suisses de Médecine Vétérinaire ASMV : la revue professionnelle des vétérinaires**

Band (Jahr): **142 (2000)**

Heft 8

PDF erstellt am: **11.09.2024**

Persistenter Link: https://doi.org/10.5169/seals-593434

# Oral immunization against rabies: afterthoughts and foresight

**A. I. Wandeler**

Rabies Centre of Expertise, Canadian Food Inspection Agency, Animal Disease Research Institute, Nepean, Ontario, Canada

**Abstract**

The article contains personal views on some issues that are frequently addressed in discussions about rabies control, and on some related topics that are often overlooked.

The first field applications of oral wildlife rabies immunization in the Swiss Rhone Valley were preceded by many years of international cooperative studies on efficacy and safety. They were significant "faits accomplis" that facilitated similar endeavors in other countries. Some aspects of the residual pathogenicity of oral rabies vaccines are discussed. The field efficacy of oral wildlife immunization is the outcome of complex interactions between vaccine and bait attributes, bait distribution procedures, and habitat properties. Significant difficulties hinder the interpretation of field observations on efficacy. Though oral wildlife immunization is not an animal welfare act and not a conservationist achievement, it is an attempt at zoonosis control intended to protect human health and prevent economic losses.

**Key words: rabies – disease control – oral immunization – vaccines – field experiments**

**Orale Immunisierung gegen Tollwut: Rückblick und Aussicht**

Einige viel diskutierte und einige vernachlässigte Probleme der Tollwutbekämpfung werden in diesem Artikel behandelt. Internationale Zusammenarbeit in zahlreichen Labor- und Felduntersuchungen und der Austausch von Informationen über die Effizienz und Sicherheit von Vakzinen haben die ersten Feldanwendungen eines oralen Impfstoffes zur Tollwutimpfung von Füchsen im Rhonetal ermöglicht. Diese ersten Feldversuche waren wichtige «faits accomplis», welche Entscheidungen zur Anwendung der Methode in anderen europäischen Ländern und in Kanada gefördert haben. Aspekte der Restpathogenität von oralen Tollwutvakzinen werden diskutiert. Eigenschaften der Vakzine und der Köder, räumliche und zeitliche Köderverteilungsstrategien, und Eigenheiten der Biotope bestimmen die Feldeffizienz der Methode. Die Schwierigkeiten der Interpretation von Beobachtungen über die Feldeffizienz werden beschrieben. Orale Wildtierimmunisierung ist keine Tierschutz- und auch keine Naturschutzmassnahme, jedoch ein Versuch zur Zoonosenkontrolle.

**Schlüsselwörter: Tollwut – Seuchenbekämpfung – orale Immunisierung – Impfstoff – Feldexperiment**

## Introduction

The following article contains personal views on some issues that are frequently addressed in discussions about rabies control, and on some related topics that are often overlooked. This is not another review of oral immunization and makes no claims on assessing the current literature. The term "oral immunization" is used when vaccine is given *per os* independent of the primary site (oropharyngeal or intestinal) of vaccine contact with immunocompetent cells.

## Rabies and rabies control

Rabies is a zoonosis. Perhaps it would be better to say: Rabies are zoonoses caused by a variety of lyssaviruses in a number of different mammalian hosts. As a disease entity with distinctive clinical and epidemiological features, it has been recognized since antiquity. However, its ranking among all human health concerns is difficult; too many imponderabilities are attached to it. It is a reportable disease in most countries, and most countries provide legislation for controlling it. Rabies control programs aim at protecting human health and preventing economic losses. The occurrence of rabies in humans can be controlled by prophylactic vaccina-

tion and postexposure treatment and 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 immunization 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.

Although a large number of mammalian species are susceptible to infection with rabies viruses, only a few are recognized 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 coadapted traits of susceptibility, viral evasion of immune surveillance, long incubation, excretion in saliva, neurological disorders that promote transmission, host life history traits, social behavior, and population biology. *Chiroptera* (bats) are identified as hosts of lyssaviruses in Australia, Africa, Europe, and in the Americas. Different *Carnivora,* including domestic dogs, are the principal hosts for classical rabies (serotype 1) in Asia, Africa, Europe, and in the Americas. From a human health and disease control standpoint one may distinguish between bat rabies, rabies maintained by terrestrial wildlife, and dog rabies.

In recent decades it has become evident that bat rabies is more widespread than originally perceived. The African, European and Australian bat lyssaviruses rarely infect humans and domestic animals. The situation is different in the Americas, where a large number of different serotype 1 variants circulate in different bat species (Brass, 1994). The impact is particularly important in the Neotropics, where haematophagous bats (vampires) frequently transmit the disease to cattle and humans. Vampire bat populations are aggressively culled, mostly after outbreaks of vampire transmitted bovine paralytic rabies (Flores-Crespo and Arellano-Sota, 1991). Though the incidence of human rabies is low in temperate North America, approximately half of the cases are due to infections with bat rabies viruses, most frequently with a virus that is associated with silverhaired bats *(Lasionycteris noctivagans).* Approaches to control the transmission of insectivorous bat rabies to people should include education of the public to avoid potentially infectious contact with bats (and wildlife in general), to seek proper treatment after exposure, and to prevent bats from establishing colonies in certain buildings (Brass, 1994).

All the principal wildlife rabies hosts of the order *Carnivora* are small to medium size omnivores, scavenging, and foraging on small vertebrates, invertebrates, fruit, and refuse produced by humans. High intrinsic population growth rates allow rapid recovery of populations decimated by persecution or disease. Wildlife rabies control by decimating host populations has been attempted in nearly all known principal host species. However, the resilience of these *Carnivora* to persecution and their reproductive potential, together with high habitat carrying capacities, often render population control efforts futile. A more promising approach is mass vaccination of the principal hosts. Indeed, oral immunization has largely replaced other wildlife rabies control strategies in Europe and North America over the past 20 years.

In large parts of Asia, Africa, and Latin America, the bulk of diagnosed rabies cases is seen in dogs. It is assumed that high density dog populations permit the occurrence of enzootic canine rabies. An estimated 20,000 to 60,000 people die of dog transmitted rabies every year. Almost all human rabies deaths and the vast majority of treated bite exposures occur in developing countries (Acha and Arambulo, 1985). Dog rabies has disappeared from most of western Europe shortly after 1900. The enforcement of responsible dog ownership has probably been instrumental. Later, dog immunization contributed to the elimination of the disease in this species from Japan and the United States (Baer and Wandeler, 1987; Larghi et al., 1988), and more recently from most major cities in Central and South America. Dog immunization campaigns are also conducted in many parts of Africa and Asia, unfortunately with much less success.

## The development of oral immunization

The idea that mass immunization of the principal wildlife hosts might be more effective than culling has emerged independently in North America and Europe. Europeans were certainly keen to adopt more humane rabies control techniques and to abandon the cruel methods of the sixties and seventies. In Europe attempts to trap wild carnivores and to release them after parenteral vaccination were rapidly abandoned, though such trap-vaccinate-release procedures are still used with apparent success in some areas of Ontario (Rosatte et al., 1992). It appears more promising to lure the wild mammal into vaccinating itself. This is possible when oral vaccines are included in baits targeted at the principal host species.

The development of oral immunization has been described a number of times (Wandeler et al., 1988b; Schneider et al., 1988; Wandeler, 1991; Winkler, 1992; Winkler and Bögel, 1992; Aubert et al., 1994; Campbell, 1994). All of these and many other accounts are chauvinistically biased to varying degrees. It is worthwhile to reconsider some

key events and circumstances. In the early 1960s George Baer found that foxes can be immunized by oral application of the live attenuated ERA (Evelyn Rokitniki Abelseth) virus. The discovery did not gather much attention until it was presented at a WHO sponsored conference to a European audience in 1970, was more accessibly published in 1971 (Baer et al., 1971), and Black and Lawson (1970) communicated similar findings. Consequently, WHO facilitated the cooperation of American, Canadian, and European research groups. The Rabies Laboratory of the Center for Disease Control in Atlanta provided ERA seed virus for studies at the "Centre de Recherche sur la Rage" in Nancy, France, the "Staatliches Veterinäruntersuchungsamt" in Frankfurt a. M., Germany, and the Swiss Rabies Center at the Veterinary School in Berne, Switzerland. The manufacturer of the commercial ERA vaccine permitted our experimentation, although we had to rename the virus to SAD (Street Alabama Dufferin). The later development of other oral rabies vaccines brought with it the new dimensions of industry involvement with property rights and patents, which has both facilitated and constrained research on oral vaccines. In 1978 the late Franz Steck, leader of the Swiss team, concluded that the time was right for a first field application (Steck et al., 1982b). This conclusion was not made without extensive data on efficacy and safety from numerous laboratory and field studies. Switzerland was joined five years later by Germany, by Italy in 1984, and by other European countries after 1985 (Aubert et al., 1994). The first field trials in the Swiss Rhone Valley were possible because of the informed courage of all the key players, which included scientists and government officials. They were significant "faits accomplis" that facilitated similar decisions in other European nations and in Canada. If we had to conduct an inaugural first field trial today, it's implementation would be constrained by a much elevated awareness of real and hypothetical risks, by much more legislation, and consequently by significantly more bureaucracy and higher costs.

## The problem of vaccine safety and species-specific efficacy

SAD/ERA viruses exhibit considerable residual pathogenicity, which resulted in the detection of three SAD rabies cases in vaccination areas in Switzerland and eight ERA rabies cases in Canada. Though this has been refuted by some researchers, there are indications that this is a general property of these strains (Flamand et al., 1989). I suspect that perceived differences in SAD/ERA pathogenicity in the field are essentially phenotypic in nature (i.e., the result of varying vaccine production protocols, vaccine titer, etc.), or are observational biases. A first attempt to remedy the pathogenicity problem was made by Flamand and co-workers. They took advantage of the observation that some escape mutants resisting neutralization by selected monoclonal antibodies also had lost their ability to cause disease in adult mice after intracerebral inoculation (Dietzschold et al., 1983). The product derived from SADBerne was given the name SAG (SAD Avirulent Gif) (Flamand et al., 1989). SAG1 was later replaced by the genetically more stable SAG2 (Lafay et al., 1994). SAG vaccines are used in Switzerland and in France for oral fox vaccination (Aubert et al., 1994).

The rapidly evolving field of molecular biology offered new opportunities. Glycoprotein is the only component of the rabies virus that induces neutralizing antibodies, though an immune response to the N-protein may also convey some protection against challenge. By the introduction of the rabies virus glycoprotein gene into the genome of a vector virus the hazards associated with attenuated rabies viruses are eliminated. No doubt, one has now to deal with another conceivable hazard: the pathogenicity of the vectored vaccine. The first recombinant rabies vaccine was developed by a working group at the Wistar Institute in Philadelphia in cooperation with commercial companies (Kieny et al., 1984). They engineered a DNA transcript of the rabies glycoprotein gene into the vaccinia virus genome, thus creating a recombinant vaccine called VRG. VRG was rigorously tested in a very large number of safety and efficacy trials at the Wistar Institute, laboratories of the Rhône Merieux companies, the "Centre de Recherche sur la Rage" in Nancy (France), the University of Liège (Belgium), and the Animal Diseases Research Institute of Agriculture, Canada. This permitted first field applications in Belgium in 1988 and in France in 1989 (Aubert et al., 1994). Rabies incidence dramatically dropped in the regions were VRG is applied.

It is possible to orally immunize foxes *(Vulpes vulpes)* with a number of live attenuated and recombinant vaccines. Oral immunization is considerably more difficult with some other potential target species, e.g., raccoons *(Procyon lotor)*, striped skunks *(Mephitis mephitis)*, and domestic dogs. One particular problem in North America is raccoon rabies, which emerged in the early 1950s in Florida. It spread from there to neighboring states, was unintentionally introduced in the late 1970s into the Mid-Atlantic Region, and is now expanding through the Appalachian range and along the Atlantic coast. Raccoons have adapted well to urban and suburban environments. The epizootic has trig-

gered important public health concerns. VRG surfaced as the logical tool to control raccoon rabies. In 1990 a first VRG field trial in the United States was conducted on Parramore Island, Virginia (Rupprecht et al., 1993). Today, the vaccine is applied in attempts to limit the spread of raccoon rabies in numerous locations in the eastern USA (Robbins et al., 1998), and it is also used in the control of coyote *(Canis latrans)* rabies (Fearneyhough et al., 1998) and gray fox *(Urocyon cinereoargenteus)* rabies in Texas.

Oral live attenuated and current live recombinant vaccines have to infect cells of the vaccine consumer in order to elicit a protective immune response. This is particularly clear with some genetically engineered vaccines, such as the human adenovirus type 5 rabies glycoprotein recombinant, where the virions do not carry the protein, but infected host cells express the inserted rabies glycoprotein gene on their surface (Yarosh et al., 1996). One may perceive hazards emerging from the fact that the vaccine viruses infect host cells. Infectious vaccine progeny may be shed into the environment. Mutants with altered pathogenicity and transmissibility may arise. These problems are addressed by inserting the glycoprotein gene into engineered vectors that are unable to complete replication in natural host cells. We have successfully induced rabies neutralizing antibodies in striped skunks by oral application of such a replication deficient human adenovirus recombinant vaccine (unpublished). Herewith we have documented that there is no need for a vector virus to produce progeny in a host as long as it introduces the rabies glycoprotein gene into cells that are capable of expressing it. One step further would be the use of killed vaccines and noninfectious peptides for oral immunization. This will not be possible before new technologies are developed to allow an efficient transfer of ingested antigens through mucous membranes to immunocompetent cells.

## The components of rabies control by oral immunization

Oral rabies vaccination programs should result in herd immunity that reduces the effective reproductive rate of the disease below unity (Anderson, 1982). What the required level of herd immunity really is, is controversial; it no doubt varies in accordance with the disease transmission dynamics in particular species and populations. I suspect that apparently successful oral vaccination campaigns frequently failed to reach the immunization levels that are advised by mathematical modelling.

The success of an oral immunization campaign depends on much more than just a potent vaccine. Figure 1 is an attempt to outline the essential components of field efficacy. Vaccine efficacy is determined in laboratory experiments, typically by following guidelines from international organizations (OIE, WHO, European Pharmacopoeia) and national legislation. We have to keep in mind that our target population in the field, affected by all kinds of immunocompromising conditions, may not be as responsive as the animals that we tested in the laboratory. Baits must be designed to release the vaccine onto a susceptible target tissue of a bait consumer. A vaccine that is inactivated by the degrading stomach environment must be delivered into either the oral cavity for infecting cells in the oropharyngeal mucosa or tonsils, or the baits (or bait

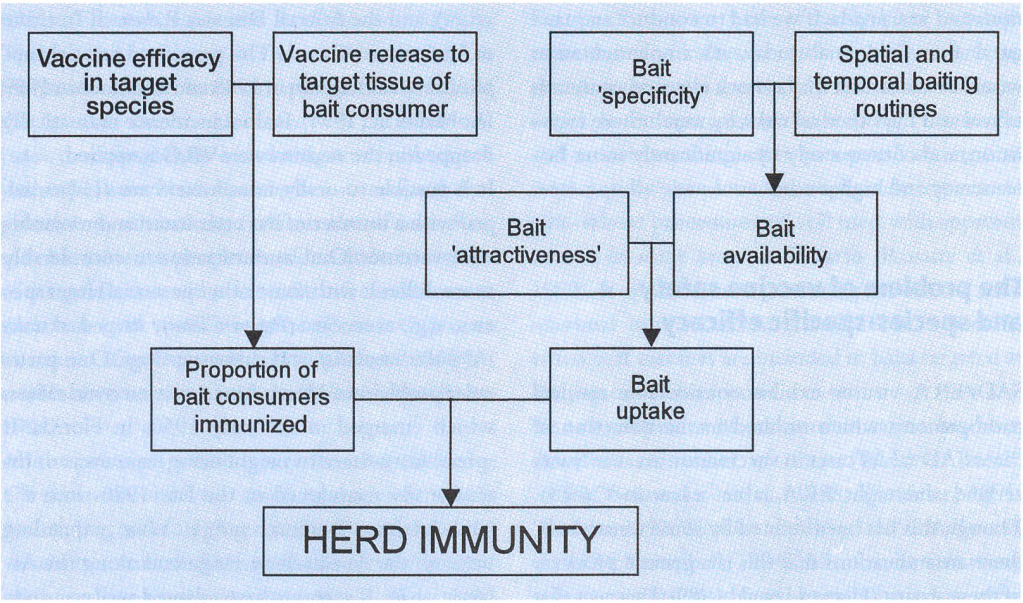


*Figure 1: The componenets of rabies control by oral immunization (see text for details).*

components) have to protect it from passage through the stomach and release it into the small intestine. A release into the intestines would have the advantage that the contact of the vaccine with intestinal mucosa would be much greater than the brief and arbitrary exposure of oropharyngeal tissues. We were surprised that antibody titers of striped skunks given an adenovirus rabies glycoprotein recombinant by endoscopy into the small intestine made significantly lower rabies antibody titers compared to skunks we had given the same vaccine by oral instillation and later realized that oropharyngeal immunization may be better than an intestinal vaccination in eliciting a systemic immunity.
Vaccine efficacy and stability, and effective vaccine release from the bait, control the proportion of bait consumers that become immunized. What proportion of the target population consumes baits within the time limits is governed by another set of conditions. Spatial and temporal distribution routines make baits available to potential consumers, though certainly differentially to different segments of the target population. Only a fraction of all baits deposited during a baiting campaign are picked up by the target species. How many are removed by competitors depends on bait specificity. But even a very specific bait may not be attractive enough to warrant sufficient bait uptake. Attractiveness of a bait changes from habitat to habitat, each offering to foragers a different range of food choices. Our understanding of the target species as "optimal foragers" lets us assume that a particular bait may be well suited for certain local and seasonal conditions only.

## Oral wildlife immunization and science

In expanding the thoughts of the previous paragraph, and also considering the constraints in our comprehension of local target populations and in monitoring immunization rates, caution should be used when interpreting possible changes of rabies prevalence in relation to oral vaccination campaigns. We are aware that sampling the host population leads to biased information (Wandeler, 1976), that antibody testing of blood samples taken from carcasses or dying animals is notoriously unreliable, and that biomarker analyses are plagued with variable backgrounds (Kappeler, 1991).
This leads to a more general question. Do we have a scientific basis for the application of oral immunization for rabies control? It is based on a number of assumptions, of which I would like to consider the following three:

1) It is possible to protect the principal host species against rabies by oral immunization.
2) There are only one or a few species that serve as principal hosts of the epizootic in a distinctive geographic area.
3) Distribution of vaccine baits brings the herd immunity in the principal host(s) to the threshold that causes rabies to become extinct.

Accepting the reality that it is impossible to prove deductively that a particular explanation is correct, we should resort to falsifying alternative hypotheses (Popper, 1959). Platt (1964) points out that we have to conduct experiments that are carefully designed to invalidate alternative explanations. This is relatively easy with the first hypothesis. Though vaccine evaluators and immunologists are not accustomed to formulating it this way, proper null hypotheses would state that the antibody profiles show no significant differences in vaccinated principals and unvaccinated controls, or that vaccinated principals and unvaccinated controls suffer indistinguishable mortality rates after challenge. Both null hypotheses can be eliminated with experiments that meet statistical requirements. We face considerably more problems with the second hypothesis. They begin with the choice and formulation of alternative theories, such as: a) all (mammalian) species contribute equally to the maintenance and spread of rabies in a given geographic area, or b) different species are variably involved, or c) the interaction of a number of distinctive key species is necessary for circulating the virus. Null hypothesis a) is disproven by showing that some species are very difficult to infect, or by documenting that the epizootic always disappears when one or a few particular species are removed from the chain of infection (e.g., by immunization). The proposed experiments, if they can be conducted at all, would not falsify null hypotheses b), c), and other alternative explanations. We meet similar problems with hypothesis three. In fact this statement is too complex and it is therefore difficult to find suitable alternative theories. But let us select one for the sake of the argument: A rabies epizootic is not affected by the distribution of vaccine baits. It is exceedingly difficult to falsify this statement. Field applications of oral immunization are not scientific experiments, they lack controls, cannot be repeated, and are difficult to monitor. "Repeats" in the same or in a different location are "pseudoreplications in space and time" (see also Hurlbert, 1984).
Should we conclude that our understanding of rabies epidemiology and rabies control is wrong because Popperian falsification does not provide satisfactory results? We are not alone in having difficulties with the hypothetico-deductive approach and explicit hypothesis testing. It is worthwhile to contemplate the discussions generated in ecology and evolutionary biology (Quinn and Dunham, 1983;

Roughgarden, 1983; Beatty, 1987; Lloyd, 1988). It is obvious that the hypothetico-deductive approach does not always contribute to the increase of scientific knowledge. Indeed, it can lead us in the wrong direction. Notwithstanding, let us remain modest: our case of rabies control in wildlife is, at best, amenable to some kind of "commonsense evaluation". I like to suggest that it becomes increasingly more believable that the distribution of vaccine baits is leading to rabies elimination when the following observations are made repeatedly. After a continuous or periodic presence of rabies over several years the disease disappears in a timely fashion, or the incidence drops significantly, following vaccination campaign implementation. Periodic prevalence peaks do not occur anymore. Advancing rabies epizootics do not penetrate into vaccinated areas while still expanding in other locations. Opposite occurrences are infrequent. It is essential that we also look for alternative explanations for the disappearance of rabies in the treated area. We should not find any that appear to be more probable. I believe that these criteria are largely fulfilled over large areas of Western Europe and in Southern Ontario in Canada. However, I like to caution from attributing too much weight to particular case histories.

## Oral wildlife immunization, ecology, and politics

Legislation and public opinion oblige national governments to combat rabies. Public pressure to achieve results is probably more intense when new epizootics emerge and spread, particularly when they threaten urban areas. All this was certainly true for Western Europe after World War II. First attempts to halt the advancing rabies front by culling its principal host, the red fox, were not very successful. Hunting and trapping alone was insufficient. Poisoning and fumigation of fox dens were introduced as additional procedures. These measures may indeed have prevented the invasion of the Danish peninsula, but had only limited impacts in other parts of Europe (Wandeler et al., 1974). Veterinary public health and public opinion changed to favoring more humane rabies control. Oral immunization was the method of choice. It soon appeared to be more successful than culling. Animal welfare aspects were important driving forces in the development and application of oral immunization of wildlife. Clearly, immunization with vaccine baits is a more humane procedure than all attempts of controlling rabies by shooting, trapping, and poisoning. However, the notion that wildlife would now be spared from dying an abhorrent death is a fallacy. Other pathogens, such as *Sarcoptes* mites, adenoviruses, morbilliviruses, etc., will take advantage of the available "substrate".

Rabies control might be perceived as a conservationist deed. No doubt, some rare species become victims of rabies epizootics upheld by more abundant species. The endangered simian jackal *(Canis simensis)*, African wild dog *(Lycaon pictus)*, and Blanford's fox *(Vulpes cana)* would probably benefit from local rabies elimination (Macdonald, 1993). However, oral wildlife immunization is not a conservation measure. Oral immunization protects the principal hosts of rabies of the order of *Carnivora* from a significant mortality factor. All these species, including domestic dogs, foxes, raccoons, jackals, and some species of mongooses, have profited enormously from agricultural and urban developments. The relationship between anthropogenic habitats and population densities of these omnivorous *Carnivora* is so obvious that one is tempted to view carnivore rabies just as one of the symptoms of this development. It is a matter of debate if rabies helps to offset other unwelcome effects of high carnivore densities, such as the spread of some other zoonotic diseases (echinococcosis, hydatidosis, etc.) and their negative impact on prey species. A number of observations suggest that host densities are indeed drastically reduced when rabies newly invades a population, and that some prey species benefit from this. But we have also noticed that rabies displaces some other mortality factors, such as sarcoptic mange in foxes. In the long run we should expect that turnover rates and demographics adjust to altered mortality patterns and that densities approach habitat carrying capacity again. When we set out to eliminate rabies, we thought we would restore the conditions prevailing before the disease invaded. Today we have become aware that habitat carrying capacities, i.e., the availability of resources, and mortality factors have changed in the meantime.

Though oral wildlife immunization is not an animal welfare act and not a conservationist achievement, it definitely is an attempt at zoonosis control intended to protect human health and prevent economic losses. Its implementation is a political decision, not a scientific one. Science can contribute arguments for and against it, and can also provide the tools for risk assessments. The arguments are primarily about vaccine safety and environmental impacts similar to the ones expressed about the release of genetically modified organisms in general (e.g., Tiedje et al., 1989). The protection of wild animals against important mortality factors affects their population dynamics and may also alter their population density. This again will bring changes for the species they prey on, their competitors, and their predators and parasites. In the case of mass vaccina-

tion, the increased host herd immunity will also exert novel selection pressures on the disease agent. One may therefore conclude that it is not wise to interfere with natural or established mortality patterns of wild animal populations. But we have to accept a few exceptions to this general rule: a) when a zoonosis is of considerable public health importance, and b) when a disease is endangering native species.

## The future: What are the problems?

What do we need for rabies control in the future? Two problems are outstanding: Rabies in dogs and in humans.

The high number of human casualties caused by dog transmitted rabies clearly indicates that dog rabies control either is not applied or is failing. There may be many reasons for not reaching a sufficient herd immunity in dog populations by parenteral vaccination: inadequate logistics, insufficient community participation, large numbers of ownerless dogs, etc. It is often thought that a majority of these problems could be solved with an oral vaccine for dogs. This notion can only be partially correct. Baits broadcasted over a landscape, as done for wildlife immunization, will reach various segments of a dog population very differentially, though other distribution models may be applied (Frontini et al., 1992; Matter, 1997). Logistics will not be simpler than with parenteral vaccination campaigns. The number of vaccine doses that do not reach the target (immunize a dog) is higher than with parenteral vaccination. The likelihood of human exposure to vaccine is much higher than in wildlife vaccination campaigns. It is therefore essential that oral rabies vaccines for dogs meet higher safety standards than those presently applied to wildlife immunization. Preference should be given to oral vaccines that consist of noninfectious antigens, to recombinant vaccines using vectors incapable of complete replication in mammalian cells, or vectors which do not have humans as potential hosts. Traditional attenuated live virus vaccines (SAD, ERA) should not be used for oral vaccination of domestic dogs.

It is obvious that the problem of human rabies would shrink considerably if the disease could be eliminated in dogs. This not being the case now, and probably not being achieved in the near future, we have to deal with rabies in humans. In view of the high efficacy of modern postexposure treatment, nearly all human cases must be considered as failures of the medical system; the correct treatment was not applied, or not applied in time. Easier access to proper treatment, simpler treatment schedules, and less expensive treatments, and last but not least, public health education would help to improve the situation. If vaccines should become inexpensive enough, one might even consider preexposure prophylaxis of larger segments of a population (e.g., children). Nonreplicating oral vaccines, possibly consisting of bioengineered antigens, could eventually play a role.

We are making progress in eliminating fox rabies from large portions of Europe and North America. Raccoon and coyote rabies control appear to become effective, but rabies in other wildlife, including bats, will persist for some time to come. Efficacious vaccines and/or appropriate vaccination technologies are not developed yet. Numerous ideas are being put forward. Some look promising, others may better not be pursued. The notion of a highly transmissible vaccine that propagates itself through a target population for circumventing some of the logistic problems is occasionally promoted. I am not in favor of allowing a genetically engineered infectious vector to spread uncontrolled in wildlife populations: not for rabies control and also not for other purposes.

There is no doubt that further technological advances will be achieved. We are already able of effectively immunizing by the oral route with nonreplicating vectors that introduce a DNA equivalent of the rabies glycoprotein gene into host cells. I see no problem in devising genetically engineered vaccines that are even more effective, safe, and selectively immunizing a narrower or wider range of target species. However, there are also formidable obstacles to such developments. Genetic engineering touches on the very substance of life. Concerns range from the sensible to the completely absurd. It is necessary that legislation addresses valid concerns and regulates the application of biotechnology. It is inevitable that legislation is occasionally a hindrance to further development. But the biggest deterrents are probably of an economical nature. Commercial manufacturers that have spent considerable resources in the development and licensing of particular products are not likely to invest more capital without relevant motivations, and they are also not likely to encourage competitive ventures.

The dreams of controlling rabies in wildlife through vaccination have become a reality. Molecular biology has led us into a new disease prevention era. However, we must consider it as a failure that the number of human rabies deaths in the world has not diminished accordingly. I am confident that progress in our understanding of all aspects of the disease could allow us to approach some of the problems more efficiently. There is also little doubt that we are in need of dialogues with other disciplines for overcoming economic and cultural obstacles to the control of a dreadful disease.

## Bibliography

A list of all references is available at the end of this issue.

**La vaccination orale contre la rage: reflexions et previsions**

L'article contient des vues personnelles sur quelques questions qui sont fréquemment posées dans des discussions sur le contrôle de la rage et sur quelques thèmes liés qui sont souvent négligés. Les premières applications sur le terrain de la vaccination orale des espèces sauvages dans la vallée du Rhône ont été précédées par plusieurs années d'études en coopération internationale concernant l'efficacité et la sécurité. Il y a eu des faits significatifs accomplis qui ont facilité des effort similaires dans d'autres pays. Quelques aspects de la pathogénéicité résiduelle des vaccins anti-rabiques seront discutés. Le vaccin, les caractéristiques de l'appât, les procédures de distribution et les propriétés de l'habitat déterminent l'efficacité sur le terrain de l'immunisation orale des espèces sauvages. Des difficultés importantes gênent l'interprétation des observations sur le terrain concernant l'efficacité. La vaccination orale des espèces sauvages n'a pas pour but le bien-être de l'animal ni une réalisation partisane de la protection de l'environnement mais bien le contrôle d'une zoonose destiné à protéger la santé publique et à prévenir des pertes économiques.

**L'immunizzazione orale contro la rabbia: ripensamenti e previsioni**

L'articolo contiene punti di vista personali su alcuni temi che vengono frequentemente affrontati nelle discussioni sul controllo della rabbia e su alcuni argomenti relativi che spesso non vengono messi sufficientemente a fuoco. Le prime applicazioni sul campo di immunizzazione orale di animali selvatici contro la rabbia nella valle del fiume Rhône sono state precedute da molti anni di studi cooperativi a livello internazionale su efficacia e sicurezza. Ci furono importanti «fatti compiuti» che facilitarono simili tentativi in altri paesi. Vengono discussi alcuni aspetti della patogenicità residua dei vaccini orali rabbici. L'efficacia sul campo dell'immunizzazione orale degli animali selvatici è il risultato di complesse interazioni tra gli attributi del vaccino e dell'esca, le procedure di distribuzione dell'esca e le caratteristiche dell'habitat. Sebbene l'immunizzazione degli animali selvatici non sia mirata al benessere animale e non sia un atto di conservazione ambientale, è un tentativo di controllo delle zoonosi al fine di proteggere la salute umana e prevenire perdite di natura economica.

**Address for correspondance**
Alexander I. Wandeler
Animal Diseases Research Institute
P.O. Box 11300, Station H, Nepean, Ontario, Canada, K2H 8P9
E-Mail: wandelera@em.agr.ca