ORAL IMMUNIZATION OF RED FOXES (Vulpes vulpes L) IN EUROPE -A REVIEW-

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AVRUPA'DA KIRMIZI TİLKİLERİN (Vulpes vulpes L) AĞIZ YOLUYLA İMMUNİZASYONU

ÖZET

Attenüe virus aşısı kullanılarak kırmızı tilkilerin kuduza karşı immunize edilebilirliğinin prensiplerini gösteren, birçok deneysel çalışmadan sonra, tilkilerin ağız yoluyla immunizasyonu ile ilgili ilk saha çalışması, 1978 yılında İsviçre'de başarıyla yürütülmüştür. Geçmişte yürütülen alışılagelmiş kuduz kontrol yöntemlerinin aksine attenüe aşıların potansiyel kullanımı, kuduzun kontrolünde yeni bir perspektif sunar görünmektedir. Bundan sonra, tilkilerin ağız yoluyla immunizasyonu modifiye canlı aşıların, bait üretim sistemlerinin, aşılama stratejilerinin ve bait dağıtımı geliştirilmesi ile ilgili uluslararası araştırmalardaki yoğun çabalardan dolayı, Avrupa'da kuduzun kontrolunda seçilen bir metot olarak gelişmiştir. Dünya Sağlık Örgütü ve Avrupa Birliği tarafından desteklenen uluslararası bir işbirliğinin sonucu olarak, tilkilerin ağız yoluyla immunizasyonu uygulamasının, katılan ülkelerde kuduzun insidansı belirgin şekilde düşmüştür. Vahşi hayvanlardaki hastalık kontrolüne yönelik bu modern yöntem, temel alınarak tilkilerdeki kuduzun yakın bir gelecekte elemine edileceği tahmin edilmektedir. Bununla birlikte son yıllarda muhtelif Avrupa ülkelerinde aşılama stratejilerindeki eksiklik ve maddi imkanlar nedeniyle, kuduz insidansında çok az bir artış görülmüştür. Bu deneyimler göstermektedir ki tilkilerin ağız yoluyla immunizasyonu ile kuduzun tamamen eradikasyonu, tahmin edilenden daha uzun sürmekte ve daha komplike olmaktadır. Bu sorunların çözülmesinde gelecekte uluslararası işbirliği (kontrol programları ve araştırmaya yönelik) son derece önemli olup, Avrupa'daki vahşi hayvanlardaki kuduzun eradikasyonu için tilkilerin oral yolla immunizasyonu amacına ulaşılması için güçlendirilmelidir.

SUMMARY

Many experimental studies showed the principle possibility of immunizing red foxes against rabies using attenuated virus vaccines. The first field trial concerning oral immunization of foxes (OIF) against rabies was successfully carried out in Switzerland in 1978. In contrast to conventional methods of rabies control conducted in the past, the potential use of attenuated vaccines appeared to offer a new perspective in rabies control. Since then the OIF has been developed into the method of choice in rabies control in Europe due to intensive efforts in international research concerning improvement and further development of modified live virus vaccines, baiting systems, vaccination strategies, and bait distribution systems. As a result of international cooperation with support of the World Health Organization and the European Union the rabies incidence has drastically decreased in OIF-participating countries. It is estimated that, with this modern method of disease control in wildlife, rabies in foxes could be eliminated in the near future. However, in recent years, several set-backs were observed resulting in a slight increase in the rabies incidence of certain European countries. These were mainly due to lack of funding and the applied vaccination strategies. These experiences indicate that the complete eradication of rabies virus with OIF is more protracted and more complicated than originally assumed. In order to solve these problems, international cooperation (control programmes and research) is of utmost importance and needs to be strengthened to reach the aim of OIF, the eradication of rabies in wildlife in Europe.

INTRODUCTION

In Europe, an epidemic of sylvatic rabies presumably spread from a focus South of Kaliningrad during the Second World War, and within a few decades conquered most parts of the continent (Wachendörfer & Frost, 1992). Due to its high susceptibility to rabies virus, the red fox (*Vulpes vulpes*) is the main reservoir and plays a critical role in the maintenance and spread of the disease in Europe. The stepwise change from urban to sylvatic rabies in the middle of the 1950s also led to changes in control policies attacking the rabies problem. In addition to the prevention of rabies in domestic animals, e.g. the vaccination of dogs and cats, the control of wildlife rabies became increasingly important (Schlüter & Müller, 1995).

It is thought that rabies in wildlife can theoretically be controlled either by an intensive reduction of the population density or by mass vaccination of reservoir populations (Aubert, 1992). The aim of conventional methods of fox rabies control was the disruption of the natural route of infection by reducing the fox density. These included attempts of hormonal sterilisation of foxes, the distribution of poison baits, trapping, digging and destroying of fox cubs at dens, den gassing and intensive culling as well. All these

methods generally were incapable of reducing the fox population below the endemic threshold and maintaining the fox population under this level (Aubert, 1992). Thus, based on many experiences, it was not possible to decrease the rabies incidence effectively by using these means.

The oral immunization of foxes (OIF) against rabies using modified live virus vaccines appeared to offer a new perspective in rabies control. The principle suitability of this method under field conditions was first successfully proven by Swiss experts in the late 1970s (Steck et al., 1978).

Since then the OIF has been developed into the method of choice in rabies control in Europe and North America. The WHO (1990a) estimated that, based on this modern method of disease control, rabies in foxes could be eliminated in Europe by the end of the 1990s.

ORAL IMMUNIZATION OF FOXES AGAINST RABIES

Historical background

At the beginning of the 1970s, Baer et al. (1971) and Debbie et al. (1972) from the Centers for Disease Control and Prevention in Atlanta, USA, first showed in experimental studies that red foxes could be immunized against rabies using attenuated virus vaccines. Subsequently, the idea of oral immunization of free-roaming red foxes against rabies using baits led to intensive work in this field of research in Europe and America. The most important research subjects were (i) the search for an effective oral vaccine, (ii) the innocuity of potential vaccines for man, target and nontarget species, (iii) the development of suitable baits and bait markers, (iv) adequate strategies and tactics for the distribution of baits and (v) epidemiological and ecological investigations of parameters pertinent to the successful eradication of rabies (MacInnes, 1988). Under the auspices of the World Health Organization (WHO), research was coordinated and accompanied by several workshops and expert conferences (Wandeler, 1988).

Field trials

The Swiss Franz Steck and his team were the first who achieved a break-through with relation to the practicability of OIF under field conditions. After Häflinger et al. (1982) had met the basic requirements for the use of the method by developing the modified live virus vaccine SAD-Bern and the chickenhead bait, the first European field trial concerning OIF against rabies was conducted in Switzerland in 1978 (Steck et al., 1982). This first vaccine-bait-system was shown to induce an acceptable immune response yielding at least 60% immune foxes in the population. A concept was developed to use natural and artificial barriers to stop the rabies epidemic, and based on this strategy the vaccination campaigns conducted

between 1978-1982 were able to free most parts of Switzerland from rabies (Kappeler et al., 1988). At the same time, efforts were made in Germany to improve the vaccine strain which resulted in the SAD B19 vaccine strain (Schneider & Cox, 1983). By contrast to SAD Bern, SAD B19 showed an improved temperature stability and was much less pathogenic for small rodents (Schneider, 1984). In Germany, the first field trial was conducted in 1983 (Schneider et al., 1983; Frost et al., 1985). Soon afterwards, the OIF was decisively pushed forward by the development of a new machine-made bait, the Tübingen bait (Schneider et al., 1987), thus meeting the requirements for a large-scale vaccination programme that was launched in 1985. At European level, oral vaccination campaigns were started in Italy in 1984 (Ruatti et al., 1988), followed by Austria in 1986 (Schmid, 1988) and by a joint project conducted in Belgium, Luxembourg and France (Pastoret et al., 1987; Artois et al., 1987). In the following years the vaccination areas were quickly extended reaching a European dimension due to the decision of the European Commission (89/455/EEC) concerning financial support of the European Community for pilot programmes on the eradication of rabies. Now, oral vaccination campaigns had to be coordinated across the borders under the auspices of the WHO. In 1988, OIF field trials were launched in Finland, the Netherlands and Slovenia (RBE, 1989), followed by the former Czechoslovakia in 1989 (Matouch, pers. comm.) and the former German Democratic Republic (Stöhr et al., 1990a). In 1992, OIF was extended in Eastern European countries. After Slovakia and Hungary, the first vaccination campaign in Poland took place in a 100 km. deep corridor along the German-Polish border in 1993 (Müller, 1997). Today, the programmes are not yet finished and in 1996 additional field trials have been implemented in Croatia and Lithuania (Cac, pers. comm.). More details concerning the history of the development of OIF, also describing the situation in North America, were published by Winkler (1992).

Rabies vaccines

The development of suitable vaccines was one of the most difficult obstacles on the way to the mass vaccination of rabies reservoirs (MacInnes, 1987). Candidate vaccine strains had to be characterized warranting high efficacy, safety, innocuity and epidemiological harmlessness as prerequisites for the success of oral vaccination campaigns. The ideal rabies vaccine for wildlife has to meet the following requirements (Rupprecht & Kieny, 1988; WHO, 1989; Wandeler, 1992a):

- capacity for successful oral immunization of the target species
- safety for target - and nontarget species (including humans)
- no shedding in excretions and secretions
- genetic stability, no reversibility to higher pathogenicity

- existence of a genetic marker
- absence of pathogenic contamination
- high shelf life and temperature stability under field conditions
- simple and inexpensive production

A detailed overview over available and tested rabies vaccines has been published by Bunn (1988) and Rupprecht & Kieny (1988). Wild animals were shown to mount an immune response after parenteral application of an inactivated vaccine. However, no wildlife species really reacted sufficiently to provide a basis for a mass vaccination, because even after booster vaccinations the seroprevalence in target species did not reach more than 30% (MacInnes, 1988). Furthermore, the suitability of inactivated vaccines in wildlife populations is limited by the required way of parenteral application.

Thus, only high-titred attenuated live virus vaccines turned out to be suitable for the oral immunization of foxes against rabies (Black & Lawson, 1980; WHO, 1982). Among these vaccines, SAD- and ERA-derived strains have been the most successful ones used under field conditions (MacInnes, 1987). A very important step for the use of attenuated live virus vaccines in the field was the possibility to distinguish vaccine strains from wildtype rabies virus using monoclonal antibodies (Schneider et al., 1983). Today, five attenuated rabies vaccines are used in Europe in oral vaccination campaigns (Stöhr & Meslin, 1996). Most of them represent SAD-strains such as SAD-Bern, SAD B19 (Fuchsoral), SAD P5/88 (Rabifox), Vnukovo 32 (Lysvulpen) (Häflinger et al., 1982; Schneider et al., 1983; Sinnecker et al., 1989; Stöhr et al., 1994; Masson et al., 1996; Artois et al., 1987). The escape mutant SAG-1 was further developed into a double avirulent derivative called SAG-2 (Lafay et al., 1994). In France, Belgium and Luxembourg a vaccinia-rabies-glycoprotein recombinant (VRG) has successfully been used in the field for many years (Blancou et al., 1986; Pastoret et al., 1988; Stöhr & Meslin, 1996). The development of VRG was the result of a joint project of Canadian, American, Belgian and French scientists (Kieny et al., 1984; Chappuis, 1992). With molecular biological tools the gene of the rabies virus glycoprotein as the crucial antigenic determinant of the virus was incorporated into the genome of vaccinia virus instead of its thymidine kinase gene (Blancou et al., 1986). The development of VRG is described in detail by Rupprecht & Kieny (1988).

Presently, none of the available attenuated live virus vaccines completely meets the requirements mentioned above. Regarding nontarget species, SAD-derivatives show a relatively low pathogenicity for distinct rodent species (Schneider & Cox, 1983; Wandeler, 1992a). It has been pointed out, however, that attenuated vaccines may sometimes revert to higher pathogenicity (Thomas et al., 1990). There are only three cases of

rabies that have possibly been vaccine induced by SAD-Bern. They occurred shortly after the beginning of field trials in Switzerland. Rabies virus isolates of a cat *(Felis catus)*, a stonemarten *(Martes foina)* and a fox cub from vaccination areas showed identical monoclonal antibody patterns with SAD-Bern, but failed to induce clinical signs in other animals (Wandeler, 1988; WHO, 1989). However, vaccine induced rabies has not been reported from any other country so far where other SAD-derivatives have been in use (Stöhr et al., 1994; Ondrejka et al., 1997).

Considering its efficacy, VRG is regarded as a revolutionary development since all species can be immunized with a sole vaccine, by while this does not hold true for attenuated live virus vaccines (Newmark, 1988; Charlton et al., 1992). Furthermore, the very high innocuity for target and nontarget species (Pastoret et al., 1988; Artois et al., 1990; Blancou & Aubert, 1992) appears to favour VRG as a potential vector virus for future rabies vaccines and the most suitable candidate for large-scale vaccination campaigns in wildlife (Pastoret et al., 1988; Thomas et al., 1990; Chappuis, 1992). However, also the use of VRG is often critically discussed. Although vaccinia virus has been successfully used for the eradication of human smallpox infections, it is known that it can cause severe illness in humans, ranging from pox lesions to lethal postvaccinal encephalitis (MacInnes, 1988). Furthermore, the incorporation of DNA fragments into non-essential regions of the vector genome may influence its pathogenicity and specifity. The fact that animal species that are normally not susceptible for the vector virus can be immunized with VRG supports this view (Wandeler, 1992b). Boulanger et al. (1995) pointed out, that a potential risk of recombination with other orthopox viruses has also to be tested. Furthermore, orthopoxvirus-specific antibodies were found in red foxes in areas where only attenuated live rabies virus vaccines had been used (Henning et al., 1995; Müller et al., 1996). It is not known, however, whether foxes carrying antibodies against orthopoxvirus can be successfully immunized against rabies using VRG, since this vaccine uses a related orthopoxvirus as the vector.

Although existing evidence suggests that the pathogenicity of attenuated vaccines for distinct model animals (laboratory rodents) is very low, a critical attitude towards attenuated live virus vaccines has recently been voiced (Stöhr et al., 1994), and refers to results of innocuity studies reporting the death of two out of four wild-trapped chaema baboons *(Papio ursinus)* after SAD-Bern was given orally (Bingham et al., 1992). However, in safety tests using SAD B19, SAD P5/88 and VRG on chimpanzees *(Pan troglotydes)*, baboons *(P. hamadryas)* and squirrel monkeys *(Saimiri sciurus)*, vaccine-induced rabies could not be demonstrated (Rupprecht et al., 1992; Neubert, pers. comm.).

BAITS

For the success of OIF, further to a suitable vaccine, the choice of the bait as the carrier for the vaccine blister is of great importance (Stöhr et al., 1990b). When developing baits, one has to consider that wild carnivores follow differing patterns in behaviour, ecology and population dynamics. Thus, a bait suitable for one species may be less attractive for others. Therefore, each reservoir species requires very specific baiting systems to maximize acceptance by the target animal and to minimize acceptance by nontarget species (WHO, 1990a). Before the era of OIF against rabies, baits were mainly tested in the context of reducing population densities of reservoir species using antifertility agents or poisons (Lewis, 1963; Balser, 1964; Linhart, 1964; Brusman et al., 1968; Oleyar & MacInnes, 1974). Baits to be used for OIF have to meet the following requirements (Wandeler et al., 1975; WHO, 1989; Stöhr et al., 1990b):

(i) Suitability as a vaccine carrier, i.e.
- no interference with vaccine efficacy
- delivery of the vaccine into the oral cavity
- resistance against unfavourable environmental and storage conditions
- protection of the vaccine under field conditions

(ii) Highly attractive, i.e.
- immediately attractive for the target species (fox)
- not attractive for nontarget species, including humans
- immediate consumption by the target species
- a high percentage of the target population should accept the bait

(iii) Suitability for industrial production
- easy and cheap production
- local availability of components

(iv) Biodegradability and safety

(v) Incorporation of a biomarker, e.g. tetracycline derivatives (250mg/bait) or iophenoxic acid (5-25mg/bait).

The chickenhead bait was the first bait out of numerous baits and attractants tested for foxes; for a review see Stöhr et al. (1990b) and Müller (1994). The chickenhead bait proved its suitability for OIF (Steck et al., 1982; Schneider et al., 1983). Nowadays, several machine-made baits consisting of fat, fish oil and fish- and bonemeal are in use (Schneider et al., 1987; Lawson et al., 1987; Brochier et al., 1988; Müller et al., 1993a).

Disappearance rate in the field and the bait uptake in the fox population represent important criteria to evaluate the attractiveness of a bait. On average, 30-43%, 60-75% and 80-93% of the baits have disappeared 3-4 days, 7-8 days and 14 days, respectively, after the distribution in the field

(Schneider et al., 1983; Brochier et al., 1987; Stöhr et al., 1990b; Müller et al., 1993a).

The most reliable information concerning the acceptance of the bait by the fox population is provided by the bait-uptake as determined by the detection of the biomarker in the bones and/or blood of animals shot (Linhart & Kennely, 1967; Larson et al., 1981; Baer et al., 1985; Johnston et al., 1987; Follmann et al., 1987). The bait-uptake can vary between 38-78% depending on the bait used, the fox density and the bait density applied in the field (Lewis, 1963; Steck et al., 1982; Wachendörfer et al., 1986; Brochier et al., 1988; Trewhella et al., 1991; MacInnes et al., 1992; Müller et al., 1993a; Stöhr et al., 1994).

VACCINATION STRATEGIES

Principles

In the past, many vaccination strategies of OIF have been studied, most of which were more or less effective. The following principal strategies turned out as basic tools in the eradication of the disease and should be applied depending on the epidemiological situation in the area to be treated.

(i) Large-scale vaccination is regarded as the method of choice as part of an initial strategy of rabies eradication (WHO, 1990a). During such a campaign the area to be treated should not be limited by administrative and political boundaries but, if applicable, rather be coordinated by cross-border activities (WHO, 1989). For the selection of vaccination areas, the size is an important criterion. At present, it is recommended that a vaccination area should at least cover 2.000-5.000 km^2, a bait density of 15 baits per km^2 provided (WHO, 1990a). We believe that the area should be as large as possible, because large-scale immunization proved very efficient when areas greater than 50.000 km^2 were treated, i.e. departments in France and whole federal states "Bundesländer" in Germany (Schlüter & Müller, 1995; Masson et al., 1996). In this case, a stepwise extension of the vaccination area after two campaigns was shown to be advantageous to use the reduced infection pressure from the areas already treated (Stöhr et al., 1994). A scrupulous and long-term enforcement provided (up to 5 years), this strategy is after all even more cost-effective than small-scale vaccination (Sehlhorst & Schlüter, 1997).

(ii) Cordon vaccination becomes increasingly important during the second phase of OIF, when it is necessary to prevent re-infection of areas already freed from rabies. This strategy characterized by the creation of a 10-30 km broad vaccination belt along a neighbouring area where rabies is still endemic. It is safe to assume that a single vaccination per year is usually sufficient, but in case of an acute and dangerous situation two vaccination campaigns per year are recommended (WHO, 1990a).

(iii) WHO furthermore favours special strategies, which are only justified under particular conditions. Spot vaccination may be used for the eradication of rabies foci after several preceding routine vaccinations, in case of given. Another special strategy is the single yearly vaccination which is only recommended for special climatic conditions and low population densities in association with low rabies frequencies (WHO, 1990a).

Selection of vaccination areas, vaccination rhythm and coverage

Due to its high capacity to adapt to environmental conditions the fox is presently colonizing all kinds of conventional and new habitats in Central Europe (including towns, parks, etc.). This poses a particular challenge for OIF-programmes, since a maximal and complete coverage of areas to be treated has to be guaranteed (Stöhr et al., 1994). For the selection of vaccination areas, topographical aspects, e.g. natural barriers for the spread of rabies, and the rabies situation in neighbouring regions have to be taken into consideration. Other selection criteria are the rabies incidence in wildlife and human exposure (Schneider et al., 1983; WHO, 1990b).

However, the question of the optimal starting point of oral vaccination campaigns is controversially discussed. Generally, vaccination campaigns should exploit the fluctuations in the rabies incidences. Vaccinations during a rabies free interval or following an incidence peak are considered most economic and efficient. By contrast, vaccination performed while the incidence of rabies is increasing may require more time and effort to be successful (Schneider et al., 1983; Artois et al., 1987; WHO, 1990a). However, it was shown in Eastern Germany that the rabies dynamic did not affect the success of OIF when large-scale vaccination was chosen (Müller, 1994; Schlüter & Müller, 1995). Usually, baits should be brought out in the vaccination areas twice a year (spring, autumn). Presently, alternative vaccination strategies are tested to further increase the bait-uptake and seroconversion in the red fox population, e.g. double vaccination within 2 to 4 weeks, den-baiting and summer vaccination campaigns. The frequency of vaccination campaigns depends on the rabies incidence and the population densities of foxes and nontarget species. Originally, it was presumed that 3 to 4 vaccination campaigns within a period of two years were sufficient to eradicate rabies (WHO, 1989). However, while in Finland only 2 to 3 vaccination campaigns were able to eliminate rabies, many more campaigns (10-12) were needed in very heavily infected regions in Germany (Westerling, 1989; Schlüter & Müller, 1995).

Bait density

To attain a satisfactory bait-uptake in target wildlife species, the different target species involved and their habitats need to be taken into

account when bait densities are determined (WHO, 1990c). In case of OIF, the bait density depends on the fox population density, its spatial distribution and social structure, food availability and the presence of potential bait competitors (nontarget species). It is presumed that in all vaccination campaigns a surplus of baits is used in relation to the fox density. Still the usual bait densities show large fluctuations; 11-15 baits/km^2 (Brochier et al., 1988; Kappeler, 1991), 15-16 baits/km^2 (Steck et al., 1982; Schneider et al., 1983; Artois et al., 1987; Schmid, 1988), 18 baits/km^2 (Müller et al., 1993a), 20 baits/km^2 (WHO, 1989; Stöhr et al., 1994) and 23 baits/km^2 (WHO, 1990c) on average. The WHO recommends a minimal bait density of 15 baits/km^2 (WHO, 1990c). An increase in bait density is recommended in case of high population densities of target and nontarget species. Considering the different baits and bait distribution strategies used in OIF, the WHO (1990a) suggested to conduct small field trials to determine the 'optimal' bait density. However, such field studies are very expensive and time-consuming.

Bait competition

Baits form an additional food-source for target and nontarget species. The bait depredation by nontarget species depends on the attractiveness of the bait for these animals and their population densities (WHO, 1990a). Therefore, the development of an efficient bait distribution strategy must also consider the seasonal and geographical differences in bait acceptance of target and nontarget species, a quantitative estimation of bait depredation by nontarget species and take potential ways of minimizing bait competition by nontarget species into account (WHO, 1990a).

During previous vaccination campaigns, many animal species have been identified as bait competitors of the red fox, e.g. rodents, mustelids, free-roaming or feral dogs and cats, raccoons, cervine species and birds, especially corvine species (Linhart, 1964; Wandeler et al., 1975; Brochier et al., 1988; Paquot et al., 1988; Stöhr et al., 1994). Basically, all carnivores and omnivores should be considered as possible bait competitors (Wandeler et al., 1975). In large areas of Central Europe, the wild boar *(Sus scrofa)* appears to be the major bait competitor (Müller et al., 1993a; Stöhr et al., 1994). In any case, the possible impact of bait competitors on OIF has to be assessed by taking their population densities into account.

Bait distribution

In the beginning of OIF, baits were predominantly distributed by hand with the assistance of local hunters (Steck et al., 1982; Schneider, 1984; Artois et al., 1987; Brochier et al., 1988). When using hand distribution, the availability of suitable maps becomes essential, to (i) define the individual vaccination areas, (ii) identify habitats outside the existing hunting-

areas, and (iii) mark the exact location of baits distributed (Stöhr et al., 1990a). A major advantage of bait distribution by hand is the possibility of hiding the baits to protect them from direct sunlight and certain bait competitors. Also, baits can be placed at locations known to be visited by foxes, thus offering the chance to influence the bait-uptake of the target species directly (Steck et al., 1982; MacInnes, 1988). Furthermore, hunters familiar with the area can adjust the bait density and distribution to local circumstances; e.g. by using higher bait densities at waste disposal sites and areas with high bait competitor densities (Stöhr et al., 1990a). The essential disadvantages of distribution by hand are the enormous expenditures in human resources, the huge amount of preliminary activities to be carried out by the veterinary authorities and hunters and the insufficient baiting of sparsely populated areas. More over, the growing weariness of hunters involved can partially explain the observed setbacks of OIF, especially in areas where successive vaccination campaigns were carried out year after year resulting in decreasing immunization rates of foxes, leading up to differences of 30% (MacInnes, 1988; Schneider, 1990; Stöhr et al., 1994).

Hence, it became necessary to look for alternatives to the existing bait distribution system, also because the size of areas to be vaccinated increased more and more. At the same time, however, the financial resources decreased. After it had been shown that baits could be distributed by airplane, this distribution system was also considered an elegant alternative in the context of OIF (Johnston et al., 1988; MacInnes, 1988; Westerling, 1989). The introduction of this cost-effective technique led to a considerable decrease in the number of preliminary activities (and the time needed to carry them out) and a qualitative improvement of the bait distribution, higher bait-uptake and immunization rate in the fox population in comparison to distribution by hand (Müller et al., 1993a). From several points of view, only certain type of planes (Cesna, Piper, Z37) with the appropriate technical prerequisites (bait-release equipment) can be used (Bachmann et al., 1990; MacInnes et al., 1992; Müller et al., 1993b). The pilots normally fly at an altitude of 30 - 150 meters above ground. Bait distribution flights in which pilots orientated themselves by using certain landmarks showed considerable course-deviations, especially during long-distance flights (Müller et al., 1993b). For instance, by using the Global Positioning System (GPS) these course deviations can be minimized. In addition, restrictions caused by bad weather can be surpassed this way (MacInnes et al., 1992). The baits are dropped from the plane either by hand or by a special bait-releasing machine. In the latter case, the number of baits dropped per time interval is directly correlated with the velocity of the plane (MacInnes et al., 1992; Müller et al., 1993b). Presently, the mechanical releasing system of baits from the plane has been optimized in such a way that the precise position where the bait was dropped can be

documented (Gschwender et al., 1996). Further details of certain aspects concerning aerial bait distribution on the required preparations, framework and field experiences have been documented (MacInnes et al., 1992; Müller et al., 1993b; Stöhr et al., 1994).

International cooperation

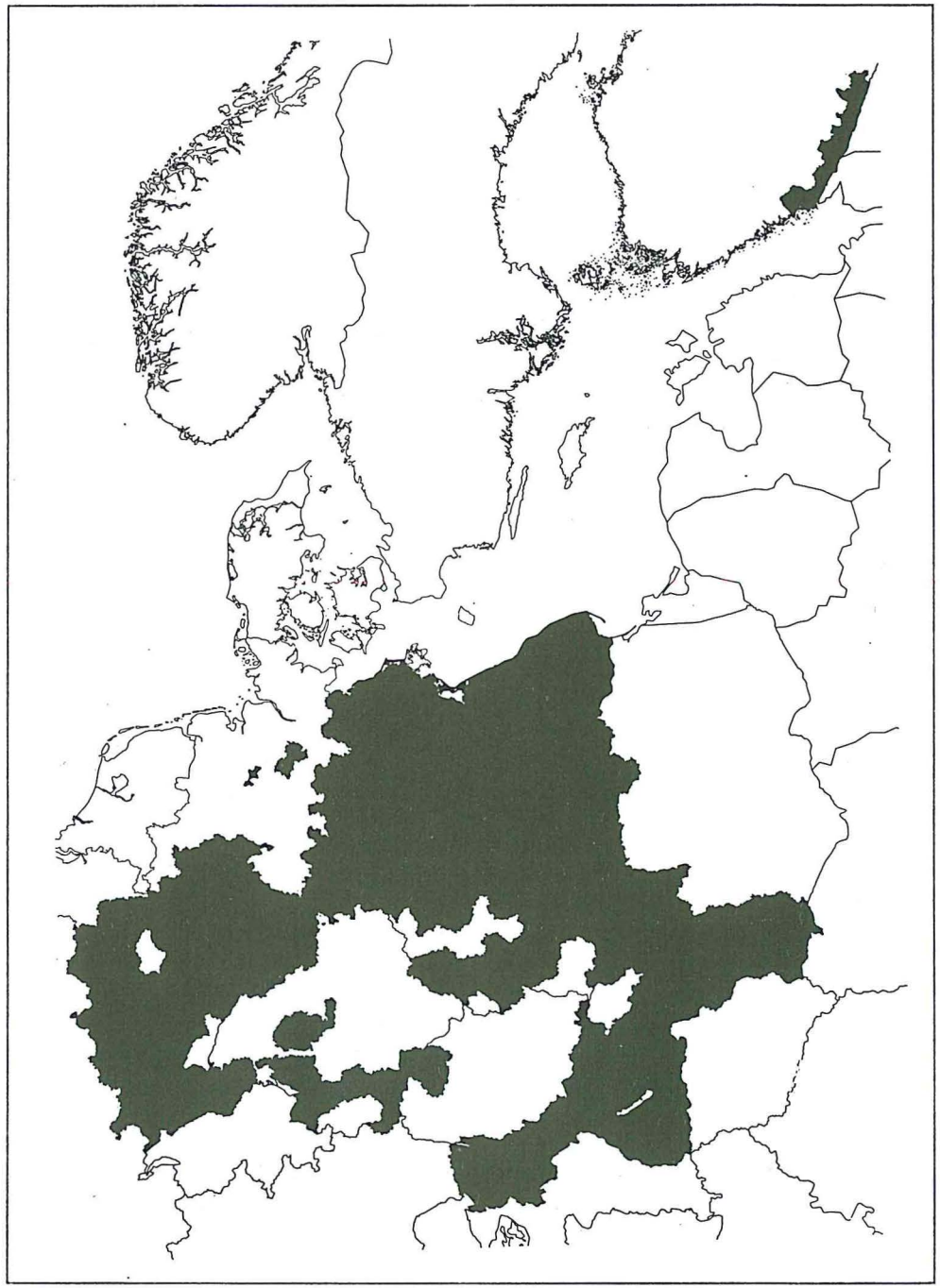
With the involvement of wildlife populations, rabies control became a global issue and international cooperation an important prerequisite to eradicate rabies. As a consequence, international organisations issued several recommendations and regulations: WHO (1990a,d), EU (89/455/EWG, 90/638/EWG, 90/424/EWG). The European Union does not only support rabies control programmes in member states, but also provides financial support to other adjourning countries. The planning, application and accounting of the required resources allocated are the responsibility of the member states involved and their neighbours. Also, annual meetings organized by the O.I.E. Reference Laboratory for Rabies (Nancy, France) and the WHO Collaborating Centre for Rabies Surveillance and Research (Wusterhausen, Germany) take place to discuss specific topics concerning rabies control in Europe (rabies diagnosis, rabies incidence and surveillance, logistics of OIF, etc.)

RESULTS OF OIF AGAINST RABIES

Without any doubt, the results achieved since the first field trials with OIF are impressive. Approximately 20 million vaccine-baits were distributed over more than 615.000 km2 in Europe in 1996 (Figure 1). As a result of intensified national and international efforts the rabies incidence has decreased drastically in OIF-participating countries (Table 1). In comparison with the classical rabies control methods (intensified hunting, gassing of fox dens, etc.) the results obtained with OIF are much better. However, the complete eradication of rabies virus with OIF was more protracted and more complicated than originally thought. In many cases, areas were declared as 'rabies-free' too early and often it was not a durable status (Schneider, 1990; Kissling & Gram, 1992; Schloss 1997).

In the past two years, different bait distribution strategies were thoroughly evaluated, and alternative strategies were brought forward and tested. Also, the existing methods for rabies diagnosis and - surveillance were reviewed and, if necessary, new ideas were implemented (Schlüter & Müller, 1995). In Germany, for instance, the rabies incidence in certain areas clearly reflected differences in vaccination strategies that had been applied in the past. In the Eastern parts of the country a rapid decrease in the number of rabies cases was observed after the implementation of OIF, while in some areas in the West severe set-backs occurred (Figure 2 & 3). Especially the insufficient cooperation in the planning of vaccination

Figure 1. Vaccination areas in Europe in 1996 (no data available for Croatia and Lithuania)



campaigns between neighbouring federal states was an important shortcoming. Similar problems have been observed in bordering areas of Belgium, Luxembourg and Germany (Saarland). More consistent progress was achieved in areas where large-scale campaigns were carried out over a prolonged period of time; however, the campaigns in these areas continued even after two 'rabies-free' years (Schlüter & Müller, 1985; Masson et al., 1996).

Table 1. Development of the rabies incidence in Central European countries where oral immunization of foxes (OIF) has been conducted.

Country	start of	Number of Rabies Cases						
	OIF	1990	1991	1992	1993	1994	1995	1996
Switzerland	1978	25	105	127	175	225	23	6
Germany	1983	5572	3597	1427	845	1378	857	152
Italy	1984	0	4	23	82	36	11	1
Austria	1986	2514	2460	1117	675	254	95	14
Belgium	1986	144	29	34	2	61	213	44
France	1986	2984	2166	1285	261	99	40	17
Luxembourg	1986	64	16	2	1	1	15	17
Netherlands	1988	22	12	8	10	1	4	5
Slovenia	1988	246	188	234	506	839	1084	247
Czech Republic	1989	1098	1097	551	422	221	178	237
Slovak Republic	1992	287	262	321	489	564	266	344
Poland	1993	2045	2287	3084	2645	2227	1973	2526

It seems that not only humans have gained from the success of OIF, but also the main victim and transmitter of the rabies virus, the red fox. With the elimination of rabies, also a very important mortality factor of the fox population disappeared. Hence, OIF did not only drastically reduce the number of rabies cases but it has also contributed to an increase in fox density (Voigt et al., 1985; Kappeler, 1992). Goretzki (1995) observed a continuously increasing fox hunting bag (number of animals killed) between 1987 and 1992. New results indicate that the fox population has multiplied in areas where OIF was carried out over a prolonged period of time (Goretzki et al., 1977). Whether the observed changes in the fox population density are exclusively a result of OIF remains unknown and disagreement on this subject is widespread among wildlife biologists (Fox, 1990). On the other hand, studies on fox population dynamics in Germany indicated an increase in fox density, irrespective of OIF (Vos, 1990). This observation is supported by other studies carried out in areas (Britain,

Figure 2. Rabies cases in Central Europe in 1990 (Source: WHO Collaborating Centre for Rabies Surveillance and Research, Wusterhausen)

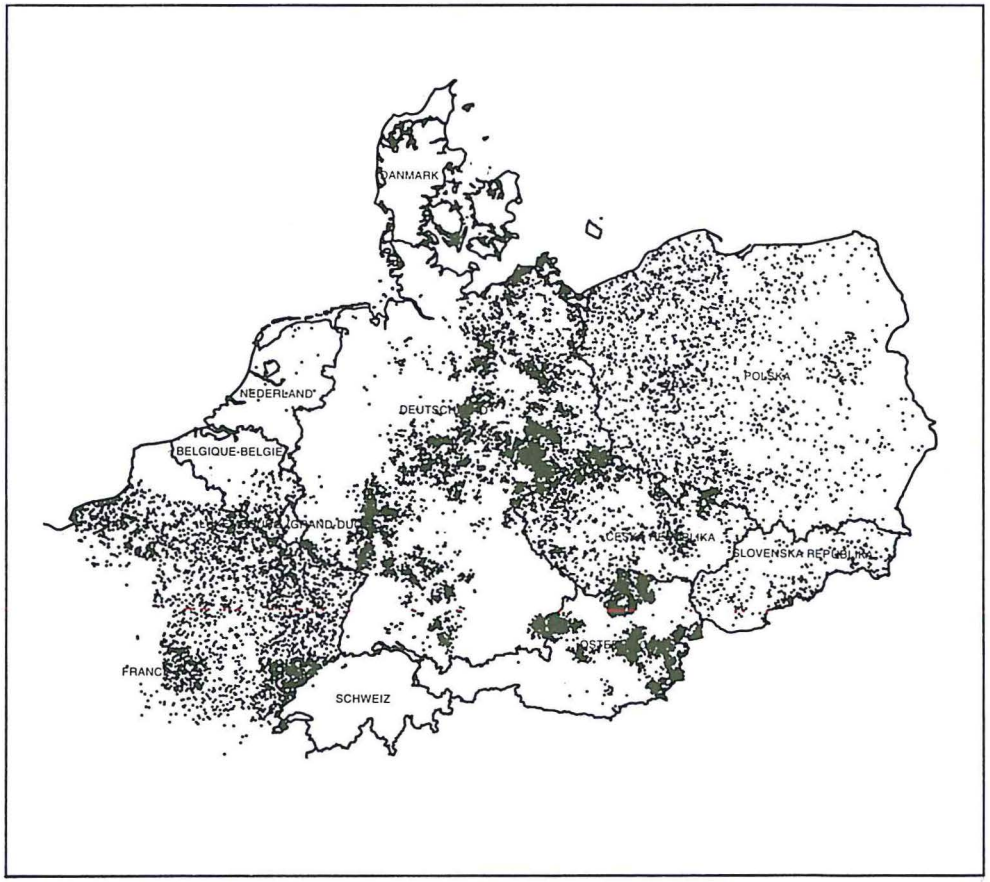
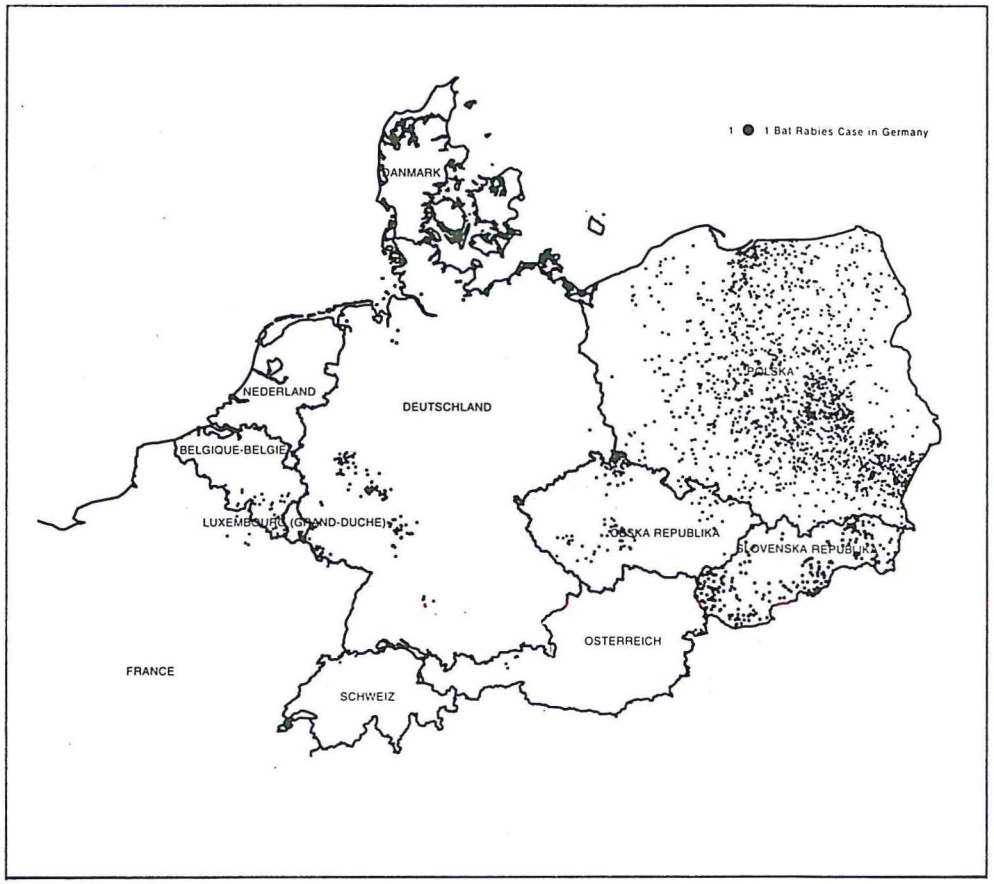


Figure 3. Rabies cases in Central Europe in 1996 (Source: WHO Collaborating Centre for Rabies Surveillance and Research, Wusterhausen)



France) which were not infected with rabies. In these areas also an increase in fox numbers was observed (Harris & Rayner, 1996a,b,c; Artois, pers. comm.). Therefore, the impact of oral vaccination on the population dynamics of the red fox could probably be best described as that of a 'catalyst' (Müller et al., 1995).

The potential impact of OIF against rabies on fox population densities has also instigated a very controversial discussion on possible effects of OIF on a postulated spread and on increasing prevalence levels of vulpine infections with the cestode *Echinococcus multilocularis*, the causative agent of human alveolar echinococcosis (Schott & Müller, 1989; Fesseler et al., 1991; Ewald, 1993; Kayerserlingk et al., 1993). This disease is considered as the most dangerous autochthonous parasitic zoonosis in Central Europe (WHO, 1990e). Whether OIF-programmes against rabies are related to an increase in the *E. multilocularis* prevalence in foxes, as observed in some areas, remains to be elucidated. It seems inappropriate, however, to question rabies control in view of the presence of *E. multilocularis* in the fox populations of Central Europe.

CONCLUSIONS

At present, the oral immunization of foxes (OIF) is without any doubt the most effective and promising method in wildlife rabies control. As a result of OIF, a partially immunized population of foxes is formed, and in conjuction with supporting activities like fox hunting the chain of infection can be interrupted. Rabies incidence does not only decrease in the fox population but also (with a temporal delay) in other animal species. The results obtained so far indicate, that OIF in relation with the different existing vaccines can eradicate rabies completely in Europe in the near future.

However, local increases in the number of rabies cases in the past years clearly indicate strategic problems in the implementation of OIF which are mainly due to (i) the size of vaccination areas which were sometimes too small, (ii) insufficient number of successive vaccination campaigns, (iii) insufficient supporting activities (hunting) and (iv) deficiencies in cross-border cooperation. All these points partially explain the increase in rabies incidence in the Czech Republic, Germany, Austria, Belgium, Switzerland, Bulgaria and Croatia. However, adequate progress and experience have recently been made by improving existing oral vaccination programmes or, if necessary, replacing them as soon as possible. Yet, there is no reason for complacency at this stage. New developments in epidemiological methods (risk assessment, computer models, cost-benefit analysis) are needed to use existing funding in an optimal way. For the continuation of OIF in Eastern Europe, a long-term financial support of the EU for the respective countries is needed. Among the 'urgent' research tasks the following issues need to be addressed soon:

- alternative OIF-strategies
- emergency vaccination programmes (reinfection, re-emerging of residual foci)
- development of criteria which allow to halt OIF-campaigns
- development of appropriate surveillance systems.

In any case, international cooperation (control programmes and research) is of utmost importance and needs to be strengthened in order to reach the aim of OIF, the eradication of rabies in Europe.

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