LIÈGE université

USE OF AN AREA INDEX TO RETROSPECTIVELY ANALYZE THE ELIMINATION OF FOX RABIES IN EUROPEAN COUNTRIES

Thomas Selhorst[1], Thomas Müller[1], Heinzpeter Schwermer[1], Mario Ziller[1], Hartmut Schlüter[1], Urs Breitenmoser[2], Uli Müller[2], Bernard Brochier[3], Paul-Pierre Pastoret[3], Franco Mutinelli[4]

[1] Federal Research Center for Virus Diseases of Animals, Institute of Epidemiology - WHO College Center for Rabies Surveillance and Research, Germany

2Swiss Rabies Center, Institute of Veterinary, VirologyUniversity of BerneBern Switzerland

3Laboraoire d'immunologie-vaccinologieFaculté de Médecine véterinaireUniversité de LiègeLiègeBelgium

4Instituto Zooprofilattico Sperimentale delle VeniceFranco MultinelliLegnaro (PD)Italy

ABSTRACT

Oral vaccination of foxes (OVF) is a powerful tool to combat rabies in wildlife, and large parts of western Europe have been freed from rabies using this tool. Nevertheless, the success of OVF, given with the number of campaigns needed to eliminate the disease, depends on many factors. This article for the first time focuses on and assesses difference in OVF with respect to the spatial setting of vaccinated areas with time. The size of the areas vaccinated with time and the size of the overlapping area of consecutively vaccinated areas are particularly considered. In order to integrate these two aspects into one single figure, an Area Index is proposed ranging between 0 and 1. A statistical analysis indicates that the number of campaigns needed for rabies elimination significantly decreases on condition that the total rabies endemic area is consecutively treated right from the beginning of oral vaccination. Hence, from an economical and environmental point of view, vaccination areas should be selected the way that guarantees an Area Index close to 1. The concept of an Area Index, as described here, is a useful tool not only in the context of OVF, but it could also be used for other control schemes against infectious diseases in wildlife.

KEYWORDS : Red fox Wildlife rabies Vaccination Area index

In Europe, an epidemic of sylvatic rabies presumably spread from a focus south of Kaliningrad during the Second World War and covered most parts of the continent within a few decades. 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.

In general, rabies in wildlife can be eliminated by disrupting the natural route of infection. It has been proposed that elimination could be achieved by lowering the density of foxes susceptible to rabies infection below a required threshold (Anderson 1986), either by reducing the fox population density or by mass vaccination (Aubert 1992). Yet, measures taken to reduce the fox population density (including hormonal sterilization of foxes, the distribution of poison baits, trapping, digging, and killing fox cubs at dens, den gassing, and intensive culling) failed to

control rabies. Mass vaccination of foxes by the oral route has emerged extremely successful and, therefore, is the preferred method for controlling rabies. Since the first field trial in Switzerland in 1978, large parts of western Europe have been freed from rabies by oral vaccination of foxes (OVF), and during the last decade, more and more eastern European countries have launched oral rabies vaccination programs or, at least, field trials (Müller and Schlüter 1998). Both humans and the fox populations benefit from this method by eliminating the risk of fatal infection.

Oral vaccination of foxes has to be conducted in an efficient way to ensure that rabies elimination is achieved. It is commonly accepted that the efficiency of OVF depends on strategic parameters defining the vaccination protocol: (1) the vaccine bait, (2) the bait density, (3) the mode of bait distribution, (4) the seasonal timing of vaccination campaigns, and (5) additional control measures like den baiting or double distribution (Schneider and others 1983; Steck and others 1985). Additionally, OVF applied in European countries during the last decades differed considerably with respect to spatial settings (i.e., the size and the selection of the vaccination areas annually). For example, in some federal states of Germany, the size and location of vaccination areas were frequently adapted in reaction to the current rabies incidence, whereas in other federal states, large overlapping vaccination areas were chosen regardless of the spatial fluctuation in rabies foci (Schlüter and Müller 1995). In Switzerland, vaccination areas were selected considering natural barriers to augment OVF (Wandeler and others 1988). On the basis of these observations, the spatial settings of OVF could result in varying OVF efficiency with respect to the length of the time needed to eliminate rabies (Schlüter and Müller 1995).

This article is intended to assess differences in the spatial settings and the effectiveness of OVF with respect to the number of campaigns needed to eliminate the disease. To quantify the spatial settings of OVFs, an Area Index (AI) is proposed that considers the size of the areas vaccinated, the continuity of vaccination in terms of the size of the area repeatedly vaccinated during consecutive campaigns, and the maximum size of the area treated during rabies elimination as conducted in four European countries.

Material and Methods

In this study, the effect of differences concerning the spatial setting of the oral vaccination campaigns against fox rabies from the beginning of the program until the elimination of rabies is considered exclusively. Possible influences of other than spatial factors will contribute to the error of the statistical model used.

Selection of Study Sites

Study sites evaluated in this analysis were situated in Belgium, Germany, Italy, and Switzerland and were selected based on the following conditions all of the data necessary for the calculation of the area index (AI) were accessible and that regions under control had been freed from wildlife rabies infection by the end of the year 2000.

Data from 19 study sites are available, comprising a nonrandom sample of OVFs conducted between 1978 and the end of the year 2000. All of the data used for analysis are given in Table 1.

The boundaries of the selected sites are either administrative borderlines or natural barriers. The geographical locations of the study sites are shown in Figures 1–4. Letters assigned to the sites correspond to the observation number (Obs) in Table 1, except for Belgium, because only one coherent area with endemic rabies is considered.

Table 1. *Data used for statistical analysis*

Table 1.   Data used for statistical analysis

Obs	Country	OVF start	y	$\overline{AI}$	vA_{max}
1	Belgium	1989 a	23	0,564	10700
2	Germany	1990 a	7	1,000	20446
3	Germany	1990 a	9	0,931	29490
4	Germany	1990 s	9	1,000	16171
5	Germany	1989 a	11	0,825	23170
6	Germany	1984 s	24	0,399	35181
7	Germany	1985 a	27	0,654	19846
8	Italy	1984 a	1	0,607	3228
9	Italy	1993 s	2	0,696	1050
10	Italy	1992 s	4	0,926	1618
11	Switzerland	1992 a	3	0,986	535
12	Switzerland	1983 a	7	0,595	3893
13	Switzerland	1982 s	10	0,335	1244
14	Switzerland	1982 s	10	0,208	1572
15	Switzerland	1983 s	10	0,390	1689
16	Switzerland	1978 a	11	0,214	983
17	Switzerland	1989 s	12	0,518	313
18	Switzerland	1979 s	16	0,244	2169
19	Switzerland	1983 a	30	0,612	5149

Note: The figures of OVF start give the year and the season (s = spring, a = autumn) when oral vaccination of foxes started. The number of campaigns conducted is given by y. The variable $\overline{AI}$ is the mean and the variable vA_{max} resembles the largest extension of the area ever treated given and is given in square kilometers.

Table 2.   Results of the statistical analysis

| Source	DF	SS (Type III)	F	$Pr > F$
vA_{max}	1	305.90	18.11	0.0009
$\overline{AI}$ (B)	1	45.19	2.68	0.1259
A × B	1	210.20	12.44	0.0037

DF = degrees of freedom, SS = sum of squares.

Table 3.   Estimated parameter figures for regression model

| Term	DF	Estimate	Std. Error	T	$Pr > \|T\|$
Intercept	1	10.46	3.092	3.384	0.0049
vA_{max} (A)	1	0.0026	0.0006	4.235	0.0009
$\overline{AI}$ (B)	1	−8.188	5.006	−1.636	0.1259
A × B	1	−0.002	0.0007	−3.527	0.0037
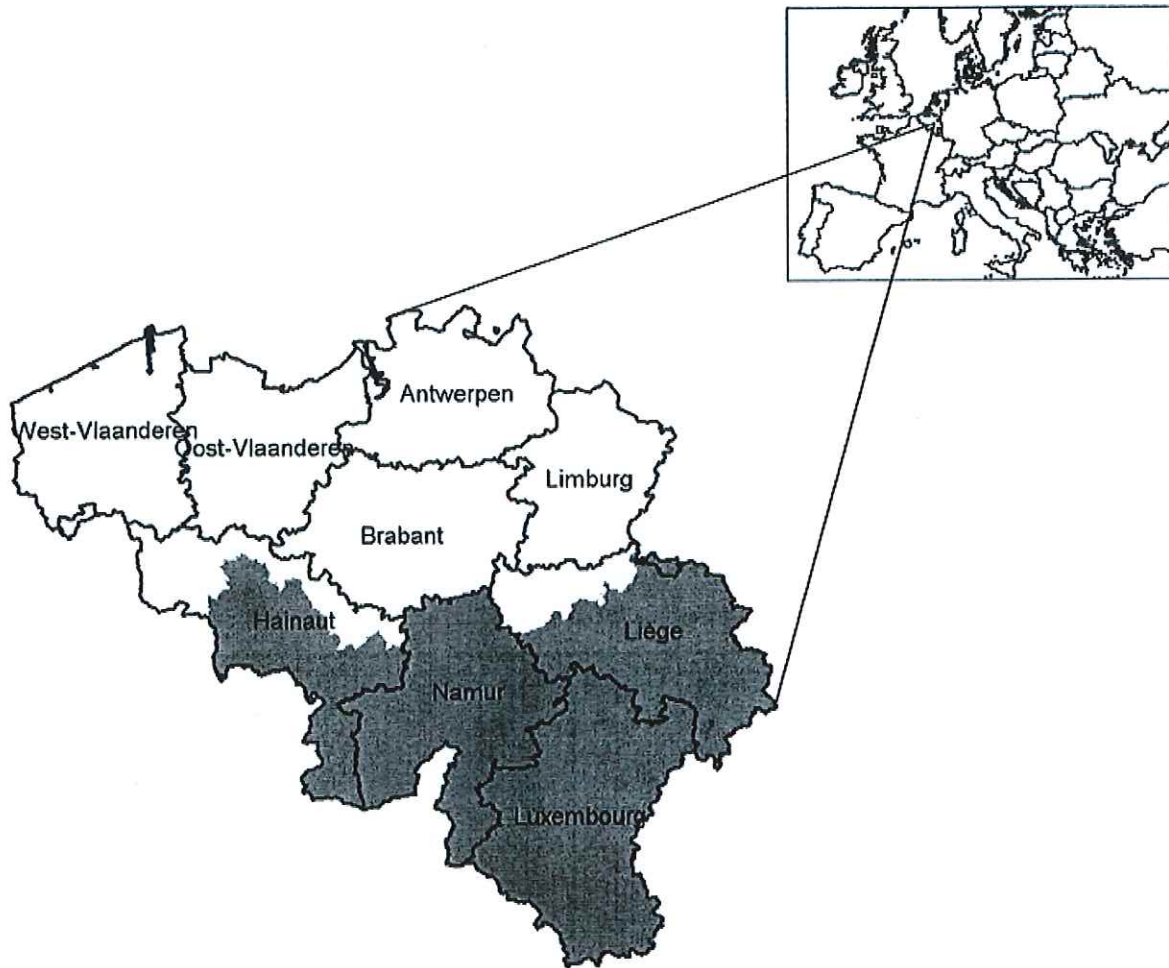
Figure 1. Rabies control in Belgium: The study site comprises the four departments of Luxembourg, Namur, Liége, and Hainaut. The shaded area represents the maximum extent of the area treated during the years 1989 and 2000.
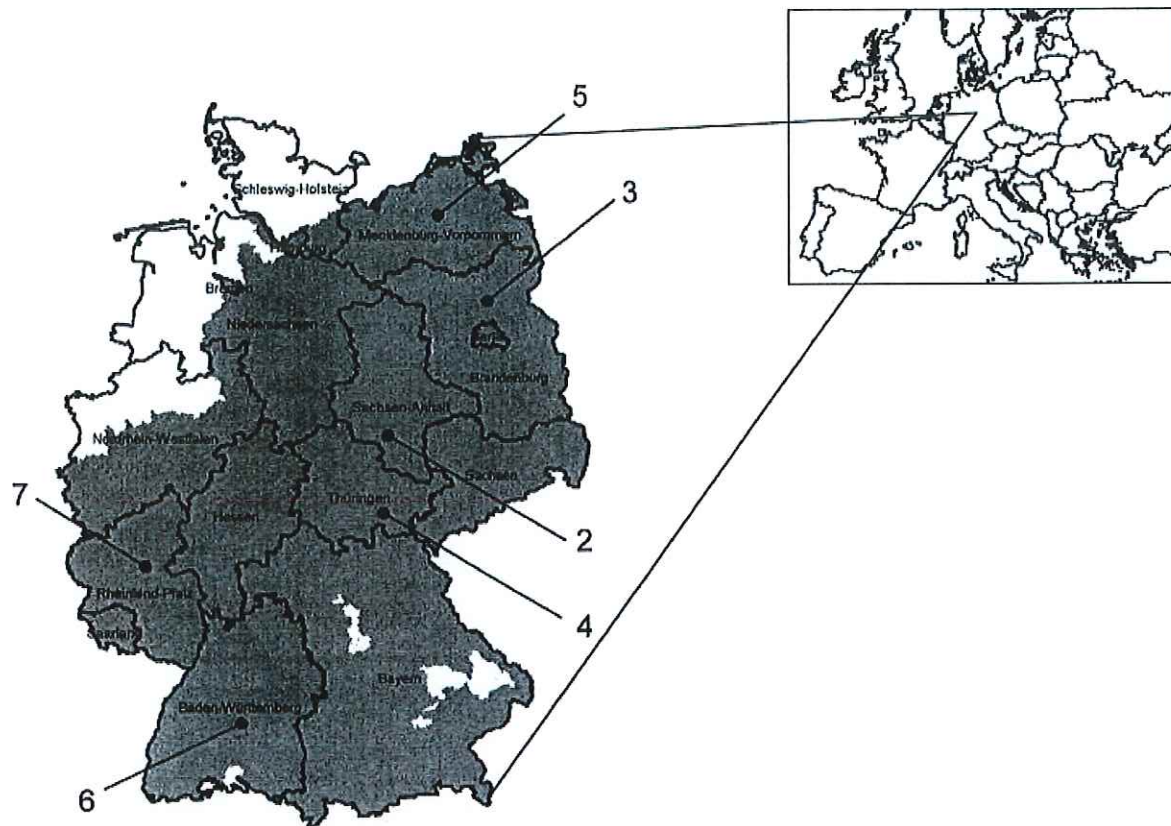
Figure 2. Rabies control in Germany: Vaccinated areas in Germany comprise the federal states of Germany except the city states of Hamburg and Bremen. The shaded area represents the maximum area vaccinated during 1983 and the end of the year 2000. Federal states that could be included in the statistical analysis are indicated by numbers corresponding to the observation number (Obs) in Table 1.
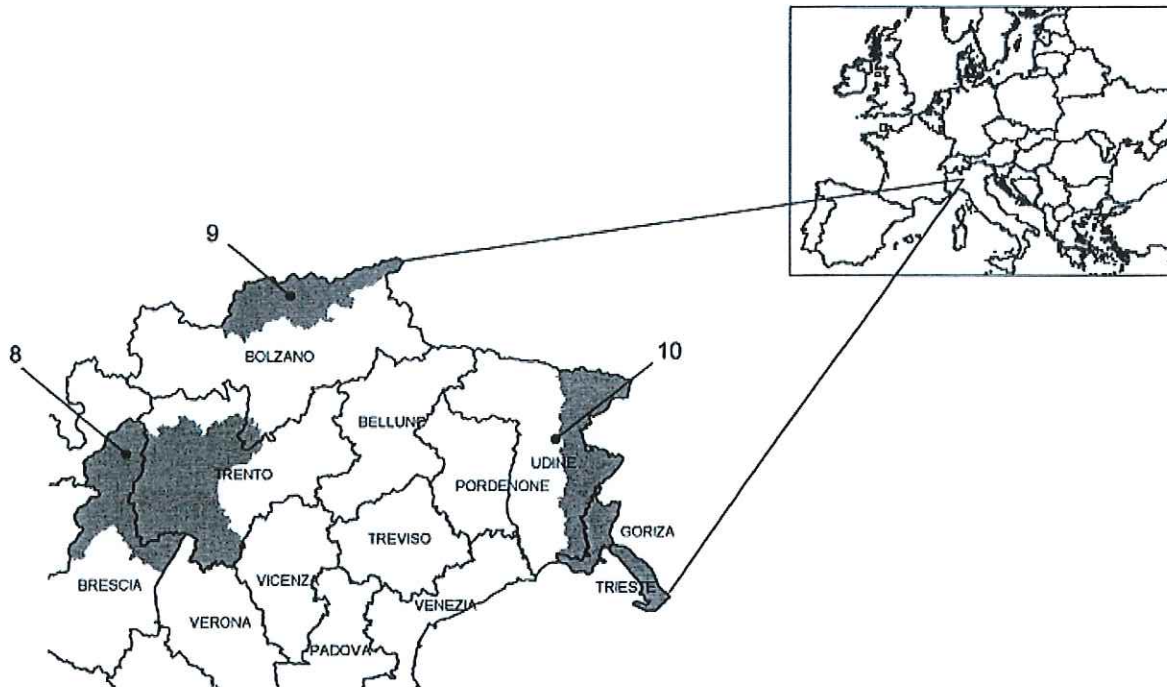
Figure 3. Rabies control in Italy: Study sites in Italy comprise parts of the six northern districts of Bolzano, Trieste, Brescia, Trento, Udine, and Goriza. The shaded area represents the maximum extension of the area ever vaccinated during 1984 and the end of the year 1995.
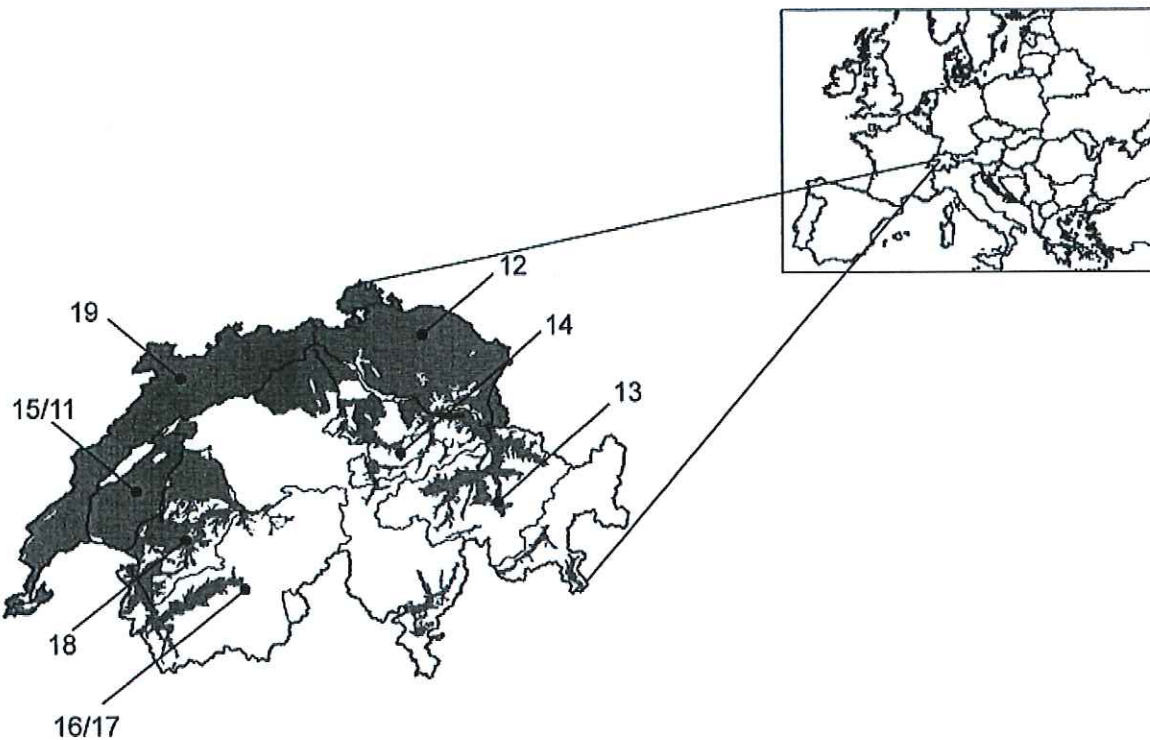
Figure 4. Rabies control in Switzerland. Study sites were formed on the basis of topographical peculiarities, resulting in bizarre patterns mirroring larger valleys of The Alps. In two regions (indicated by dual numbers), oral vaccination of foxes had been conducted two times with an adjournment of 5 years and of 2 years, respectively.

In Belgium (Figure1), the OVF targeted one coherent area with endemic rabies. This study site comprises the abutting departments of Luxembourg, Namur, Liége, and Hainaut (Pastoret and Brochier 1999; Brochier and others 2001).

In Germany, rabies was endemic in most parts of the country (Müller und Schlüter 1998). Because the federal states are responsible for rabies elimination using OVF, the administrative regions (i.e., the federal states) represent the study sites in Germany (see Figure 2).

In Italy, rabies occurred in three spatially and/or temporally separated endemic foci in the northern parts of the country. OVF was thus independently targeted for each focus (Vos and others 2000). Three study sites located in the districts of Bolzano, Trieste, Brescia, Trento, Udine, and Goriza were included in the analysis (Figure 3).

Due to the geological distinctiveness of Switzerland (high reaches of The Alps), natural topographical boundaries (see Figure 4) determined the shape of the areas where OVF was conducted, leading to areas with a small extension (Wandeler and others 1988; Kappeler and Wandeler 2000). To overcome the problem that the Swiss study sites were too small for comparison with larger ones of other European countries, neighboring compartments were merged, resulting in larger, coherent areas where OVF has been conducted.

Information concerning the size and the location of the area vaccinated per campaign has been provided either by the national veterinary authorities or by the WHO Collaborating Centre for Rabies Surveillance and Research in Europe. For each vaccination campaign, the location and the size of the vaccinated areas were identified as follows : If printed maps of the vaccinated areas were available, these maps were digitized and the area covered by vaccination was calculated using a geographic information system (ArcView 3.1, ESRI). If the location and the size of the vaccinated areas were available on the basis of the vaccination status of municipalities, the size of the vaccinated areas were calculated using data on the size of the municipalities with the help of a mapping program (Regio-Graph 2.0; Macon Waghäusel, Germany).

Vaccination Protocols

A standard vaccination protocol was applied in the study sites with respect to the following:

- The seasonal timing of the bait distribution (two times a year in spring and autumn)
- The bait density (12–25 baits per square kilometer on average)
- The mode of bait distribution (hand or aerial distribution)
- The maximum flight line distance of about 1 km in the case of aerial distribution.

Sometimes, vaccination protocols diverged from the standard protocol as follows : Occasionally, additional campaigns were conducted either in summer or in winter. These campaigns are not considered in this study. With respect to two Italian regions (Brescia and Trieste), campaigns were conducted only once a year in spring because of the specific epidemiological situation. This special case is considered during statistical analysis.

Differences in the vaccination protocols existed with respect to the rabies virus vaccine used, but it is assumed that the efficacy of the vaccines used is comparable. In Belgium, the attenuated rabies virus vaccine SAD B19 was applied between 1986 and 1990, which had subsequently been replaced by the vaccinia glycoprotein recombinant rabies vaccine (VRG) (Brochier and others 1988; Pastoret and Brochier 1999). With respect to the other study sites considered in the analysis, attenuated rabies virus vaccines were used exclusively, such as SAD Bern (Switzerland), SAD B19 (Germany, Italy), SAD P5/88 (Germany), and SAG 2 (Switzerland) (Steck and others 1982; Müller and Schlüter 1998; Bruyere and others 2000; Breitenmoser and others 2000; Vos and others 2000).

Calculation of the Area index

An Area Index (AI) is proposed in order to quantify differences in the spatial setting of the vaccination campaigns with time. The AI i with respect to campaign i is given by

$$\mathrm{AI}_i = \frac{vA_i}{vA_{i-1}} \frac{dA_i}{vA_{\mathrm{max}}} (i > 1)$$

where vA_i is the size of the vaccinated area during campaign i $vA_i > 0$ $\forall i$, vA_{i-1} is the size of the vaccinated area during the preceding campaign i–1, dA_i is the size of the area vaccinated during the campaigns i as well as i–1 (i.e., the intersection between two consecutive campaigns), and vA_{max} is the size of the area that had to be treated from the beginning of OVF to the elimination of rabies. Given the area indices for each campaign i, the mean area index ($\overline{\mathrm{AI}}$) for the whole observational period is readily calculated.

The figures of the $\overline{\mathrm{AI}}$ are limited to the range from 0 to 1. An $\overline{\mathrm{AI}}$ of 0 can only occur if the vaccination areas of consecutive campaigns do not overlap (i.e., $dA_i = 0$ $\forall i$). An $\overline{\mathrm{AI}}$ close to 0 would indicate that overlapping was limited and that the proportion of the vaccinated areas over the size of the area of the study site was systematically small. The mean AI is equal to 1 if the vaccinated area vA_i equals vA max during consecutive vaccination campaigns i.

The AI has been calculated for each of the above-mentioned study sites (see Table 1).

Rabies Status and Number of Vaccination Campaigns Conducted

The number of rabies cases for each study site was recorded for time periods between consecutive vaccination campaigns. Because every rabies case outside an actual vaccination area leads to an extension of this area in the following campaign, all rabies cases recorded

originate from the vaccination area ever treated, vA max. Therefore, vA max characterizes the entire rabies endemic area.

The number of vaccination campaigns conducted for each study site was recorded. By definition, rabies is assumed to be eliminated (i.e., status of a region under control is "rabies free") if the disease has not been reported within a 2-year surveillance period following the last confirmed rabies case. Typically, up to four additional vaccination campaigns have to be conducted during this period (WHO 1989; Tischendorf and others 1998). However, because in some study sites vaccination had been terminated earlier, the number of campaigns was calculated from the beginning of OVF until the last rabies case had occurred.

Statistical Methods

The number of vaccination campaigns conducted (y) is the dependent variable in the statistical analysis and is used to quantify possible efficiency differences of the vaccination protocols.

The $\overline{\text{AI}}$ quantifies differences between the vaccination protocols with respect to the spatial settings. Possible influences of additional strategic parameters [i.e., the vaccine baits used, the bait density applied, the mode of bait distribution (hand/aerial), or alternative vaccination protocols (den baiting/double baiting)] are not considered in this analysis.

Because we consider the fact that for two Italian regions (Brescia, Trieste) vaccination was only conducted once a year, two statistical analyses are done. The first one includes these regions and the second one excludes study sites comprising these regions (i.e., observations 8 and 10 in Table 1).

A multivariate regression analysis using the mean AI ($\overline{\text{AI}}$) and the area ever treated (vA max) as continuous influential variables is performed with the help of the SAS V8.0 statistical software. Main effects and interactions between the AI and the area ever treated are tested.

Results

The data used in the statistical analysis are given in Table 1.

Descriptive Statistics

The earliest OVF campaigns started in autumn 1978 (observation 16) in a limited part of Switzerland and the latest in 1993 (observation 9) in the district of Bolzano (Italy). The number of campaigns conducted until rabies elimination ranges from 1 campaign to 30 campaigns, with a median number of 10 campaigns.

The extension of the area ever treated (vA max) ranges from 313 to 35,181 km2, with a median extension of 3228 km2. The mean area indices range from 0.21 to 1.0, with a median of 0.61.

Multiple Regression Analysis

In order to eliminate the outlier distortion on the statistical results, an outlier test based on the standardized residuals is performed and observations 6 (influential observation) and 19 (outlier) are to be excluded from the analysis.

The analysis indicates that there is strong statistical evidence ($\text{Pr} > \text{F} = 0.0009$) that the explanatory variables in the model are related to the expected value of y (number of campaigns conducted). The interaction between $\overline{AI}$ and uA max is significant. The adjusted coefficient of determination for this analysis equals 0.64.

The Type III sum of squares and the parameter estimates of the model are given in Tables 2 and 3.

The predicted model for the number of campaigns conducted is

$$y = 10.46 - 8.188\overline{AI} + 0.0026 vA_{\text{max}} - (0.002\overline{AI})vA_{\text{max}}$$

The statistical analysis indicates a significant interaction between $\overline{AI}$ and vA max, that is, the effect of the spatial setting of the vaccination areas with time depends on the size of the area ever treated (vA max). When vA max is large, then the effect of $\overline{AI}$ on the number of campaigns to be conducted to eliminate rabies is also large, and vice versa.

In Italy, there are two study sites where oral vaccination campaigns have been conducted only once a year. This protocol differs from all of the other protocols conducted in the other sites and it is important to analyze the effect of whether the exclusion of these two sites alters the statistical results obtained so far.

Exclusion of the study sites denoted Obs 8 and 10 in Table 1 does not alter the statistical results obtained earlier. Again, a significant interaction between $\overline{AI}$

and vA max is observed and the parameters of the predicted model differ slightly from the above model; that is,

$$y = 10.6 - 7.03\overline{AI} + 0.0026 vA_{\text{max}} - (0.003\overline{AI})vA_{\text{max}}$$

Discussion

Circumstantial evidence suggested that the spatial settings of OVF could result in differences concerning the length of time needed for eliminating rabies (Schlüter and Müller 1995). In this article, we use an AI as part of a statistical model to assess, for the first time, the influence of the strategic selection, size, and continuity of vaccinated areas upon the time needed to eliminate rabies in selected study sites across western Europe. This study focused exclusively on the effect of spatial differences in the vaccination protocols ; hence, other influential parameters such as the efficacy of the vaccine baits, minor differences in the general vaccination protocol (e.g., timing of the vaccination campaigns and the method of aerial distribution of the baits, etc.), as well as differences in the fox densities, ecological conditions, and the intensity of the rabies surveillance are not considered. The influence of these variables is expected to contribute to the error term of the statistical model.

A multivariate regression analysis using the size of the study area and the $\overline{AI}$ as influential variables was set up to explain differences in the time needed to eliminate rabies in wildlife. The results of the statistical analysis indicate that the two selected influential variables indeed explain 64% of the variation in the independent variable (coefficient of determination = 0.64). Hence, this finding indicates that the spatial setting of vaccination campaigns indeed does have an important influence on the success of oral vaccination campaigns.

However, in the present study, it was not possible to randomly select regions under rabies control for the statistical evaluation. One main criterion for the selection of study sites was that rabies had been eliminated by the end of the year 2000. However, in some regions of Europe, rabies elimination using OVF is still in progress or has just started. Thus, it might not be possible to draw general conclusions from the present study. Nevertheless, the analysis confirms the assumption that the strategic selection, size, and continuity of vaccinated areas have influenced the time needed to eliminate rabies in the study sites considered in this analysis.

Number of Campaigns Needed for Fox Rabies Elimination

When OVF was implemented in Europe, it was assumed that four consecutive vaccination campaigns might be sufficient to eliminate rabies in a given area (WHO 1989). However, in the present study, only 4 out of 19 study sites were rabies-free after 4 campaigns at maximum. Although other regions in Switzerland (not included in our study) needed only 7 months from the start of OVF (Kappeler and Wandeler 2000), our data clearly indicate that, in general, a median number of 10 campaigns (e.g., 5 years) is necessary for rabies elimination. This is in accordance with the 12 vaccination campaigns proposed by Tischendorf and others (1998) thus suggesting that favorable topographical features might have contributed to an early local extinction of rabies in some Swiss regions, as assumed by Breitenmoser and others (2000).

Furthermore, the number of campaigns needed for elimination in a particular region is also influenced by the rabies situation in neighboring regions, which, again, is influenced by rabies-control measures in those regions. This can be a risk factor for rabies elimination, and under adverse circumstances, it can result in massive reinfections. The influence of

reinfections on the duration of the elimination of rabies in small Swiss regions is well described (Breitenmoser and others 2000). In the Saxony region of Germany, for example (Figure 2), the maximum area treated from the beginning of OVF until the end of the year 2000 was 18,412 km2, with an AI of 0.866. After 14 campaigns vaccination was stopped in the northern parts. However, an increasing rabies incidence in the neighboring region of the Czech Republic resulting in permanent reinfection along the Czech–Saxonian and Polish–Saxonian border forced the veterinary authorities to safeguard the federal state by establishing a vaccination belt in those border areas. These measures decreased the AI for the whole period, and the region under control failed to become rabies-free during the observation period (Schaarschmidt and others 2002). These examples clearly indicate that it is essential to coordinate cross-border activities independent of administrative borders at an international and/or national level (WHO 1989). Part of the success of Belgium, France, Luxembourg, and Switzerland in controlling fox rabies was due to the fact that they developed close cooperation for preventing cross-border contamination and improving their vaccination techniques (Aubert and others 1994).

The present analysis indicates that the AI is a helpful measure to explain differences observed in the efficacy of OVFs (expressed by the number of campaigns conducted), which are based on differences in the strategic selection, size, and continuity of vaccination areas. Another influencing factor is the time point at which a region is declared rabies-free. Often, vaccination areas were declared "rabies-free" too early, resulting in a nondurable status that, in the end, was followed by a protraction of rabies elimination (Schneider 1990; Kissling and Gram 1992). Because it has been shown that rabies can persist under vaccination on a very low level, forming moving clusters in space and time, it was recommended to continue vaccination at least for 2 years (four campaigns) after the last rabies case in a particular region to guarantee a likely success (Tischendorf and others 1998).

In literature, it is also speculated that additional measures might influence the number of campaigns to rabies elimination, such as summer vaccination (Masson and others 1999; Selhorst and others 2001) or fertility control in the target population (Stöhr and Meslin 1997; Smith and Wilkensen 2003). It is obvious that additional measures capable of increasing the percentage of vaccinated foxes would contribute to an earlier elimination of rabies. However, additional measures have to be integrated into the overall concept of rabies elimination, because a singular measure cannot be expected to be successful. Also, fertility control remains ecologically questionable because of considerable side effects on nontarget species.

Area Index

Based on observations concerning spatially different vaccination areas in Germany, it was speculated that the design of a vaccination area substantially influences the number of campaigns needed in order to eliminate rabies (i.e., the success of vaccination campaign) (Müller and others 1993; Schlüter and Müller 1995). In the western federal states of Germany, OVFs were frequently adapted to the current rabies incidence resulting in a patchy pattern of vaccination areas changing from vaccination campaign to vaccination campaign. In contrast, in the eastern parts of Germany, OVFs were practiced on a large scale, covering the entire area of the federal state in each campaign (Schlüter and Müller 1995). The assumption that

this resulted in considerable differences in the success of OVF programs is verified by the results obtained with this analysis.

The AI ranges from 0 to 1. The broad spectrum of the AI values (range = 0.208–1.0) calculated for the 19 study sites considered in this analysis clearly shows that the selection and continuity of the vaccination areas varied considerably (see Table 1). Based on the results of the statistical analysis, it is concluded that the strategic selection and continuity of vaccination areas influences the number of campaigns needed to eliminate rabies, particularly when the maximum area to be treated is large. Based on the results obtained, a high AI index correlates with fast rabies elimination, whereas a low AI is an indicator for a prolongation of rabies elimination.

The ecological background for this statistical finding is given by the population dynamics of the red fox. The fox population dynamics resembles a birth pulse dynamics ; the fox cubs are given birth in spring. Hence, a part of the population is exchanged by newborn animals every year. Especially during this time period, the vaccination coverage is expected to drop to figures below the required coverage for rabies elimination (i.e., 70%) (Anderson 1986). Only in areas with a high AI can a permanent high vaccination coverage (percentage of protected foxes) be induced by the application of repeated vaccination campaigns. This compensates for the population turnover and finally interrupts the rabies infectious chain. Therefore, it is indeed important to vaccinate areas repeatedly in order to guarantee a permanent high vaccination coverage. Therefore, it is recommended to repeatedly cover even small regions completely from the first vaccination campaign onward.

Size of Vaccinated Areas

It is evident that the size of a region to be vaccinated depends on the rabies situation. For example, if a whole region is highly endemic, as was the case in the federal states of eastern Germany (Figure 2), the region to be vaccinated has to be as large as the size of the federal states. If, however, rabies is endemic only in a limited part of a region to be freed from rabies, the area to be vaccinated can be smaller (see, e.g., Belgium and Italy; Figures 1 and 3). However, unfavorable strategic decisions concerning the selection and the size of vaccination areas could make it necessary to increase the size of the area to be vaccinated due to an increase of rabies cases resulting from an unexpected spreading of the disease, which might even run out of control. Reasons leading to such unfavorable decisions might be financial considerations, shortcomings in long-term planning of OVF, and/or insufficient rabies surveillance in nonvaccinated areas adjacent to vaccinated areas, as observed in some western German federal states (Schlüter personal communication).

Rabies elimination should be more likely, simply by chance, in regions of small sizes. However, it is recommended that the minimum size of an area to be vaccinated should be 2000 or 5000 km2 (WHO 1989; Thulke and others 2000) and the minimum size for an area to be declared rabies-free should measure 6000 km2 in size (WHO 1989). Most of the small study sites considered in the present analysis are located in the Swiss or Italian Alps. They could, thus, have benefited from mountain barriers, which might hamper the spread of rabies from one area to the other (Wandeler and others 1988). If natural barriers cannot be used,

OVF should be designed on a large scale, resulting in vaccination areas of at least 50,000 km2 (Carius and others 1990). Elimination will likely take longer under these circumstances.

In larger countries, rabies endemic regions might be too large to be treated completely from the beginning of OVF due to logistic reasons or funding difficulties. Therefore, large-scale OVF might not be practical, requiring new strategies to be developed. One possibility could be a systematic step-by-step vaccination, shifting the vaccination areas from those already considered free from rabies at a certain time point to those areas still contaminated until the elimination of the disease in the whole region is reached. Such a strategy has been applied in France (Bruyere and Janot 2000). Another possibility could be a ring vaccination, starting from the fringe and margins, moving toward the center of the rabies infested area to be controlled. In both cases, an overlap of the shifting vaccination areas is required.

Conclusions

Based on the results of the present analysis, it is stated that wildlife rabies management (OVF) requires a coherent spatial and long-term approach. When planning OVF, decision-makers should budget financial resources for at least 5 years in advance. Furthermore, the size of the vaccination area should be as large as possible, provided an area index close to 1 is guaranteed during subsequent years. Using this strategy, relatively high costs arise at the beginning of OVF. However, on the long run, money is expected to be saved. In regions too large for complete coverage, the same areas should be vaccinated several times until rabies elimination is achieved, and newly vaccinated areas must overlap the region already covered by vaccination to such an extent that reinfection of the area already freed from rabies is prevented.

The Area Index method illustrates that wherever these commonsense principles were followed, vaccination programs were more successful and required a smaller number of vaccination campaigns and were, hence, also cost-efficient. However, these conclusions are valid only if the fox is the one and only reservoir for rabies in a region. If other reservoir species are present, this might require specially adapted strategies for rabies control with respect to vaccine baits, the seasonal timing of bait distribution, the spatial setting of bait distribution, and other factors.

Acknowledgments

References

Anderson, R. 1986. Rabies control. Vaccination of wildlife reservoirs. Nature 322(6077) :304–305.

Aubert, M. 1992. Epidemiology of fox rabies. Pages 9–18 in K. Bo"gel, F. Meslin, and M. Kaplan (eds.), Wildlife rabies control. Wells Medical Ltd., Kent U.K.

Aubert, M., E. Masson, M. Artois, and J. Barrat. 1994. Oral wildlife rabies vaccination field trials in Europe, with recent emphasis on France. Pages 219–243 in C. E. Rupprecht, B. Dietzschold, and H. Koprowski (eds.), Current topics in microbiology and immunology. Volume 187. Springer-Verlag, Berlin.

Breitenmoser, D., U. Mu"ller, A. Kappler, and R. Zanoni. 2000. Die Endphase der Tollwut in der Schweiz. Schweizer Archiv für Tierheilkunde 142:447–454.

Brochier, B., I. Thomas, A. Iokem, A. Ginter, J. Kalpers, F. Costy, and P. Pastoret. 1998. A field trial in Belgium to control fox rabies by oral immunisation. Veterinary Record 123(24):618–621.

Bruyere, V., and C. Janot. 2000. La France bientôt déclarée officiellement indemne de rage. Bulletin épidémiologique mensuel de la rage animale en France 30(10–11–12):1–2.

Bruyere, V., P. Vuillaume, F. Cliquet, and M. Aubert. 2000. Oral vaccination of foxes with one or two delayed distributions of SAG2 baits during the spring. Veterinary Research 31:339–345.

Carius, H., V. Gutho"rl, and P. Mu"ller. 1990. Raumnutzung und Mobilita"t des Vektors Fuchs. Pages 99–106 in C.

Commichau and H. Sprangel. (eds.), Fuchssymposium, Koblenz. Volume 20. Verlag J. Neumann-Neudamm, Melsungen, Germany.

Kappeler, A., and A. Wandeler. 2000. Entwicklung von Strategien zur Feldanwendung der oralen Immunisierung von Füchsen gegen Tollwut. Schweizer Archiv fu"r Tierheilkunde 142(8):439–446.

Kissling, R., and G. Gram. 1992. Orale Immunisierung von Fu"chsen gegen Tollwut in O" sterreich im Zeitraum von 1986–1991. Wiener Tieara"ztliche Monatsschrift 79:333–344.

Masson, E., V. Bruyere-Masson, P. Vuillaume, S. Lemoyne, and M. Aubert. 1999. Rabies oral vaccination of foxes during the summer with the VRG vaccine bait. Veterinary Research 30(6):595–605.

Müller, T., and H. Schlu" ter. 1998. Oral immunization of red foxes (Vulpes vulpes) against rabies—A review. The Journal of Etlik Veterinary Microbiology, Ankara 9:35–39.

Müller, T., K. Sto"hr, J. Teuffert, and P. Sto"hr. 1993. Oral immunization of foxes against rabies: Experience with aerial distribution of baits. Deutsche tiera"rztliche Wochenschrift 100:203–207.

Pastoret, P., and B. Brochier. 1999. Epidemiology and control of fox rabies in Europe. Vaccine 17(13–14):1750–1754.

Schaarschmidt, U., T. Mu"ller, G. Albert, A. J. Muluneh, C. T. Selhorstv, and H. Schlu" er. 2002. Erfahrungen mit der Begleitdiagnostik zur oralen Immunisierung der Füchse in Sachsen unter besonderer Beru"cksichtigung einer standard-isierten Tollwutserologie. Deutsche Tierarztliche Wohenschrift 109:219–225.

Schlüter, H., and T. Mu" ller. 1995. Tollwutbeka"mpfung in Deutschland—Ergebnisse und Schlußfolgerungen aus über 10-jahriger Bekampfung. Tierarztliche Umschau 50:748–758.

Schneider, L., G. Wachendo"rfer, E. Schmittdiel, and J. Cox. 1983. Ein Feldversuch zur oralen Immunisierung von Füchsen gegen die Tollwut in der BRD. ii. Planung, Durchführung und Auswertung des Feldversuches. Tierarztliche Umschau 38:476–480.

LIÈGE
université

Schneider, L. G. 1990. Der Einfluss der oralen Immunisierung der Füchse auf die Epidemiologie der Tollwut. Pages 154–164 in C. Commichau, H. Sprangel (eds.), Fuchs Symposium Volume 20. Verlag J. Neumann-Neudamm, Melsungen, Germany.

Selhorst, T., H. Thulke, and T. Mu¨ ller. 2001. Cost-efficient vaccination of foxes (Vulpes vulpes) against rabies and the need of a new baiting strategy. Preventive Veterinary Medicine 51(1–2):95–109.

Smith, G. C., and D. Wilkinson. 2003. Modeling control of rabies outbreaks in red fox populations to evaluate culling, vaccination, and vaccination combined with fertility control. Journal of Wildlife Disease 39(2):278–286.

Steck, F., A. Wandeler, P. Bichsel, S. Capt, and L. Scheider. 1982. Oral immunisatioin of foxes against rabies. Zentralblatt für Veterina¨rmedizin, Reihe B 29:372–396.

Steck, F., A. Wandeler, P. Bichsel, S. Capt, U. Ha¨fliger, and L. Schneider. 1985. Oral immunization of foxes against rabies. Laboratory and field studies. Comparative Immunology, Microbiology and Infectious Disease 5:165–171.

Sto¨hr, K., and F. X. Meslin. 1997. Zoonoses and fertility control in wildlife—Requirements for vaccines. Reproduction, Fertility, and Development 9(1):149–155.

Thulke, H.-H., L. Tischendorf, C. Staubach, T. Selhorst, F. Jeltsch, T. Mu¨ ller, H. Schlu¨ ter, and C. Wissel. 2000. The spatio-temporal dynamics of a postvaccination recovery of rabies in foxes and emergency vaccination planning. Preventive Veterinary Medicine 47:1–21.

Tischendorf, L., H.-H. Thulke, C. Staubach, M. Mu¨ ller, F. Jeltsch, V. Grimm, J. Goretzki, T. Mu¨ ller, H. Schlu¨ ter, and C. Wissel. 1998. Chance and risk of controlling rabies in large-scale and long-term immunised fox populations. Proceedings of the Royal Society of London Series B 5:839– 845.

Vos, A., T. Mu¨ ller, P. Schuster, H. Schlu¨ ter, and A. Neubert. 2000. Oral vaccination of foxes against rabies with SAD B19

in Europe, 1983–1988. A review. Veterinary Bulletin 70(1):1– 6.

Wandeler, A., S. Capt, H. Gerber, A. Kappler, and R. Kipfer. 1998. Rabies epidemiology, natural barriers and fox vaccination. Parasitologia 30(1):53–57.

WHO. 1989. Report of the WHO consultation on requirements and criteria for field trials on oral vaccination of dogs and wild carnivores. World Health Organisation, Geneva.