

# Efficacy of the first oral vaccination against fox rabies in Slovenia

A. CURK \* and T.E. CARPENTER \*\*

**Summary:** *Fox population reduction was the first measure undertaken to control rabies in foxes, but this proved unsuccessful. The promising results of oral immunisation of foxes against rabies in some European countries encouraged the authorisation of the first rabies vaccination of foxes in the field in Slovenia, in October 1988. In the present study, intervention analysis is used to evaluate the results of this vaccination campaign. The analysis took into account the cyclic nature of fox rabies and the possible effects of variability in the fox carcass submission rate. The results confirmed the decrease in fox rabies after the launch of the vaccination campaign. The reduction was independent of both cyclic oscillations in fox rabies and variability in carcass submission rate, thus indicating a positive net effect of the vaccination.*

KEYWORDS: Epidemiology – Foxes – Rabies – Slovenia – Vaccination.

## INTRODUCTION

The current fox rabies epidemic in central Europe commenced in Poland during the Second World War and has gradually spread to most central and western European countries, and eastward into the former Soviet Union (3). The red fox (*Vulpes vulpes*) is both the reservoir of rabies infection and the major vector species (5). Rabies infection prevalence in foxes is strongly dependent on population density and turnover, and the contact rate between foxes (2, 5, 11, 12, 22, 30, 37). However, the relationship between fox density and rabies occurrence is non-linear (21). Initial control measures were directed at a reduction in fox populations, with the aim of reducing density below the threshold level required for the persistence of the infection. Continued culling is required to maintain an area free from rabies, and the implications of this cost must be considered when the disease is rare (3).

The first rabies case of the current epidemic in Slovenia was diagnosed towards the end of 1973. At that time, the epidemic was restricted to the eastern region of Slovenia by natural geographical barriers. A second wave of infection came from Austria in 1979, and spread throughout the country within a few years. Subsequently, fox rabies has represented a constant threat to the human population and domestic animals in this area.

A new era of fox rabies control has now commenced, following the discovery that foxes can be immunised by the oral route (8). The promising results obtained from field

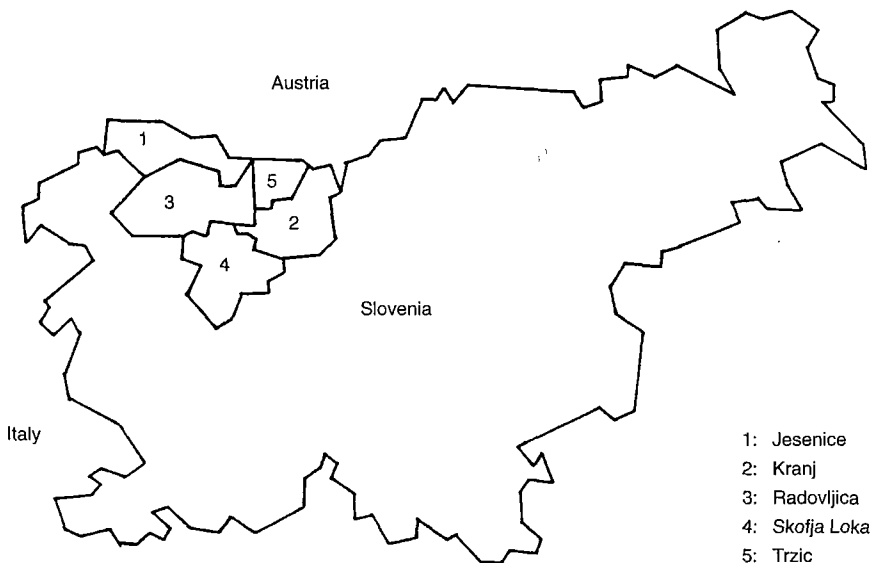
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trials on oral immunisation of foxes in western and central Europe (10, 16, 17, 24, 35, 38, 39) encouraged the first field vaccination of foxes in Slovenia. A region of 540 km<sup>2</sup> named Gorenjska (Fig. 1) was approved for vaccination; the total area of the Republic of Slovenia is 20,259 km<sup>2</sup>. The region of Gorenjska is largely covered with forest (59% of land use), while 35% of land is used for agriculture (44). In October 1988, 8,800 (16.3 per km<sup>2</sup>) Tübingen fox baits (32) containing live attenuated Street Alabama Dufferin (SAD) B19 virus and tetracycline as a biomarker were laid by volunteer hunters. The vaccination campaign followed the Bavarian model (32, 33, 43) and was repeated the following spring and autumn. Further regions participated over the next four years, until all of Slovenia was covered by 1992. After each bait distribution, hunters were asked to observe bait uptake on days 4, 8 and 14 after distribution. Hunters were also asked to provide samples of foxes killed four to six weeks after each successive bait distribution; these were examined using tetracycline and serological (rabies antibodies) methods at the World Health Organisation Reference Centre in Tübingen, Germany. Average bait uptake, as observed by hunters in Gorenjska, was approximately 60%. Tetracycline was found in 36-58% of the foxes examined, while antibodies were detected in 38-86% of the foxes, depending on the year and season.

As mentioned above, vaccination is not the only factor which may influence rabies spread among foxes. In the absence of rabies, fox populations seem to increase up to a characteristic density ( $K$ ) determined by the carrying capacity of the habitat. Theoretically, a threshold density ( $K_T$ ) exists, below which endemic persistence of rabies cannot be maintained (9). An outbreak arises when  $K$  is significantly larger than  $K_T$ , because  $K > K_T$  implies that  $R > 1$  (where  $R$  is the basic reproduction ratio of infection) (4). At the height of an epidemic, rabies may kill up to 50% of the fox population (12). However, the population is capable of rapid recovery (41) and may even overshoot the



**FIG. 1**

**Map of Slovenia, showing the five communities of Gorenjska where fox vaccination was first performed in the field**

original population level within three to seven years (3, 12, 22). Disease outbreaks thus tend to be cyclic, and cycles of 3.75 years are present in Slovenia (20).

As the region of Gorenjska was the pilot region for the vaccination campaign for foxes in Slovenia, the purpose of this study was to determine whether the vaccination campaign significantly reduced rabies incidence among foxes in the region between October 1988 and June 1992.

## MATERIALS AND METHODS

### Definition of 'cases'

In Slovenia, all hunters are requested to send carcasses of all foxes shot or found dead to the laboratory of the Veterinary Faculty at the University of Ljubljana. Samples are taken at autopsy from the Ammon's horn of each fox, and these are examined for rabies presence. A 'case' of rabies is thereafter defined as a specimen which has been tested and found positive by direct immunofluorescence (23).

### Study design

The time series of the monthly totals of positive cases in Gorenjska between January 1980 and June 1992 served as the primary data base. In the follow-up period, a total of 602 positive cases occurred per month (average 4.01; range 0-46). Table I presents the numbers of fox samples submitted and found positive for rabies in the region each year between 1980 and 1992. The change in the mean number of fox rabies cases before and after the beginning of the vaccination campaign could be tested by means of the

TABLE I

*Annual numbers of fox samples submitted for rabies diagnosis in Gorenjska, Slovenia*

Year	No. of samples submitted	No. (%) of positive samples
1980	274	84 (30.66)
1981	463	185 (39.96)
1982	81	22 (27.16)
1983	64	14 (21.88)
1984	52	11 (21.15)
1985	83	1 (1.20)
1986	42	0 (0.00)
1987	101	18 (17.82)
1988	285	154 (54.04)
1989	179	87 (48.60)
1990	100	19 (19.00)
1991	93	7 (7.53)
1992 *	46	0 (0.00)

\* first half of the year only

Student's *t* test. However, as the time series of fox rabies in Gorenjska is serially correlated and expresses cyclic variations, the use of dynamic intervention models was preferred. These dynamic intervention models are based on ARIMA (Autoregressive Integrated Moving Average) models (14) and were introduced by Box and Tiao (15).

To mark the pre- and post-vaccination periods, a dummy intervention variable was formed. The coefficient of this variable is of greatest interest in the present study.

Fox population density should be considered when analysing the effects of vaccination. Unfortunately, no reliable fox population density estimates are available. However, as the dynamics of fox population density may be assumed to be implicit in the cyclic patterns of fox rabies outbreaks (5, 11, 37), the time series of fox rabies cases in Slovenia was used as a proxy variable for the dynamics of the fox population in Gorenjska. However, the validity of the above assumption cannot be proved, and hence a note of caution is necessary here.

Another source of variation – variability in fox carcass submission rate – should also be included in the models. The number of carcasses submitted to the laboratory for testing is a limiting factor and can influence the incidence figures obtained (6). Rates of monthly submissions were therefore offered as the third explanatory variable in the analysis.

### Analysis

Analyses were conducted using the SAS (Statistical Analysis System) computer package (36) and the corresponding ARIMA procedure. The following three steps were involved:

- identification of the model
- estimation of parameters
- modelling validation.

Classical Box-Jenkins models describe stationary time series. Intuitively, a time series is stationary if the statistical properties (e.g. the mean and the variance) of the series are essentially constant through time (13). Following the Box and Jenkins (14) methodology of model identification, it was apparent that the time series under consideration was not stationary. The original non-stationary time series was therefore transformed into a stationary time series:

$$y_t = Y_t - Y_{t-1} \quad (\text{equation 1})$$

(where  $y_t$  denotes the stationary fox rabies time series;  $Y_t$  is the original non-stationary time series; and  $Y_{t-1}$  is the same non-stationary time series lagged by one time period).

The time series of fox rabies in Slovenia ( $X_{1t}$ ) and the series of submission rate ( $X_{2t}$ ) were included in the model to account for the fox population dynamics and the variations in submission rate, respectively. The value of the intervention variable (vaccination:  $I_t$ ) is equal to 0 up to the month when the vaccination began, and equal to 1 thereafter. Relationships between the variables  $X_{1t}$ ,  $X_{2t}$ ,  $I_t$  and the output variable  $y_t$  may be represented via a function – generally named the transfer function (B) – which, for the present purposes, may be represented as follows:

$$v(B) = \omega B^b \quad (\text{equation 2})$$

(where  $\omega$  measures the effect of the input variable on the output variable;  $B$  is the lag operator; and  $b$  is the number of periods before the input series begins to affect the

output series [dead-time]. The lag operator  $B$  is introduced for notational convenience; it shifts time one or more steps back, thus:  $BX_t \equiv X_{t-1}$ ,  $B^b X_t \equiv X_{t-b}$ , etc.).

$X_{1t}$  and  $X_{2t}$  will not perfectly explain  $y_t$ , so there is a need to include a 'noise' (error) component,  $N_t$ , of the following form (19):

$$(1 - \phi_1 B - \phi_2 B^2 - \dots) N_t = (1 - \theta_1 B - \theta_2 B^2 - \dots) a_t \quad (\text{equation 3})$$

which can also be presented as follows:

$$N_t = \frac{\theta(B)}{\phi(B)} a_t \quad (\text{equation 4})$$

(where  $\theta$  is a moving average parameter;  $\phi$  is an autoregressive parameter; and  $a_t$  is 'white noise'). The choice of moving average and autoregressive parameters is based on the sample autocorrelations and partial autocorrelations considered as autocorrelation and partial autocorrelation functions of the lag  $k$  (25). The form of the two functions serves as means of identifying moving average and autoregressive parameters.

Thus, predictions of the output variable are based on its own history and its relation to the input variables. To find the component of  $y_t$  explained by each input variable ( $X_{1t}$ ,  $X_{2t}$  and  $I_t$ ), the input variables are filtered through the respective transfer functions. Finally, the noise is filtered through the noise function.

In the present case, the dynamic transfer function/noise model – which relates the output variable  $y_t$  to the input variables  $X_{1t}$ ,  $X_{2t}$ , to the intervention variable  $I_t$  and to its own history – is formulated as follows (equations 2 and 4):

$$y_t = \mu + \omega_1 B^b X_{1t} + \omega_2 B^b X_{2t} + \omega_3 B^b I_t + N_t \quad (\text{equation 5})$$

(where  $\omega_1$  and  $\omega_2 > 0$ ; and  $\omega_3 < 0$ ). In terms of regression analysis, the input variables  $X_{1t}$ ,  $X_{2t}$  and  $I_t$  correspond to explanatory variables, while the noise component  $N_t$  (autoregressive, moving average parameters and 'white noise') represents the structure of the underlying time series.

Inspection of autocorrelation, partial autocorrelation and cross-correlation functions (28) then reveals the particular form which the transfer functions and the noise model will take.

The crucial assumption made in the transfer function/noise model is that the  $X_t$ 's and  $N_t$  are independent, so that past  $X$ 's influence future  $y$ 's, but not vice versa.

Parameters in the model were estimated using the conditional least-squares method (36). Ljung-Box chi-square tests (27) were performed for the autocorrelations in the residuals and for the cross-correlations between input  $X_t$ 's and the residuals. The final model is a result of several iterations of the identification/estimation/checking process, and meets the conventional criteria for model adequacy (27).

## RESULTS

The final transfer function/noise model includes two transfer function parameters, an intervention parameter, two moving average parameters and an autoregressive parameter (Table II).

The step intervention variable has the value  $I_t = 0$  before the commencement of vaccination and  $I_t = 1$  afterwards.

**TABLE II**  
*Estimated parameters of the fox rabies occurrence model*

Variables	Estimate	Standard error	T ratio	P value
Explanatory variables:				
$X_{1t}$	0.073	0.008	8.87	<0.001
$X_{2t}$	0.186	0.022	8.39	<0.001
$I_t$ , shift 5	-3.539	1.634	-2.17	<0.05
Time series parameters ( $N_t$ ):				
Moving average, lag 1	0.532	0.078	7.31	<0.001
Moving average, lag 3	0.185	0.073	3.42	<0.001
Autoregressive, lag 5	-0.258	0.091	-2.83	<0.01

The estimated constant term ( $\mu$ ) was not included in the model, as this was not statistically significant, implying that there is no deterministic linear trend. The model fit is illustrated by Figure 2.

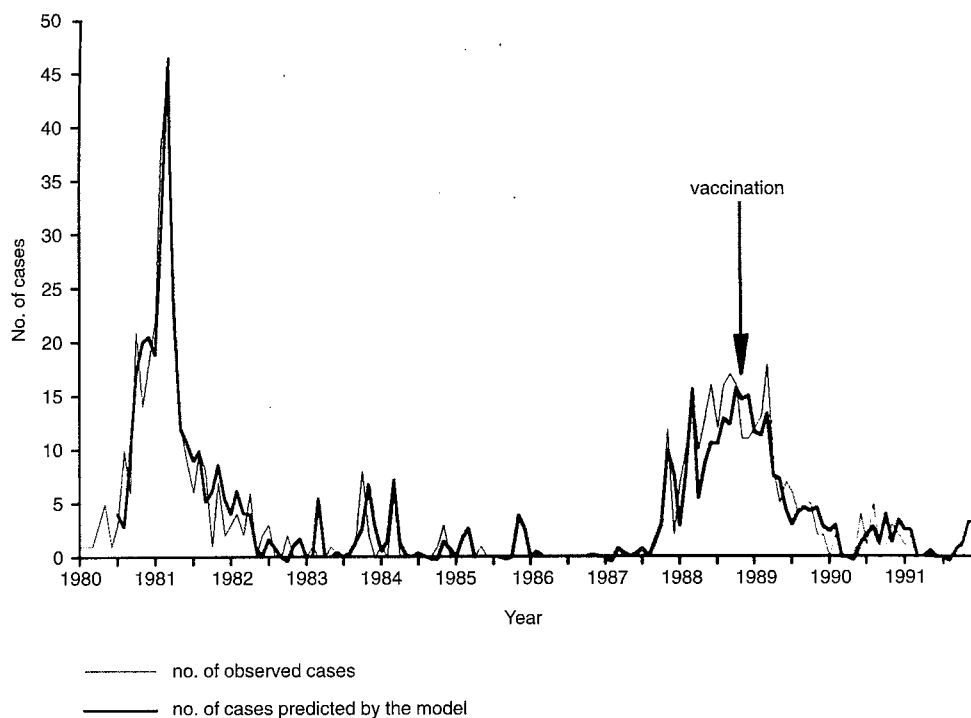
The parameter of the intervention variable is negative and the parameters of the other two input variables are positive, as expected. The intervention parameter shows an average significant reduction of 3.4 rabies cases per month ( $P < 0.05$ ) compared to the pre-vaccination period; this could be associated with the vaccination. The campaign began in October, and a step response to the vaccination appeared five months later (shift 5 in the intervention variable as mentioned above). The correlations among the model parameters are negligible. An autocorrelation check of the residuals to the lags 6, 12, 18 and 24 (performed automatically by the SAS package) resulted in statistically insignificant autocorrelations as tested by the Ljung and Box (27) method. In addition, a cross-correlation check of the residuals with the input  $X_t$ 's to lags 5, 11, 17 and 23 revealed no specification errors in the model. The estimated standard error of the model is equal to 2.408.

## DISCUSSION

Controlling for both cyclic oscillations in fox rabies and variation in submission rate, the intervention parameter represents the net effect of the vaccination. The results indicate that the 'delay' parameter of the intervention variable is equal to 5, i.e. the vaccination took statistically-significant effect five months after it commenced. Although the first observable results coincided with the time of the second bait-laying campaign, these can be attributed to the first campaign. Reports from some European countries show that the number of rabies cases can be drastically reduced following a single vaccination (26, 34, 40).

For each additional sample tested, approximately 0.2 ( $P < 0.001$ ) rabies case is diagnosed if the other three model variables are held constant. The parameter of the variable submission rate is found to be statistically significant; this is not surprising, as the submission rate is a limiting factor.

The number of positive cases in Gorenjska was found to be dependent on the cyclic oscillation of fox rabies incidence throughout Slovenia ( $X_1$ ), and thus indirectly dependent on fox population density. For each new case diagnosed in Slovenia, 0.07 ( $P < 0.001$ ) case was diagnosed in Gorenjska.



**FIG. 2**

**Comparison of observed and predicted numbers of fox rabies cases in Gorenjska between 1980 and 1991**

The three coefficients of the noise model are necessary to take advantage of the information absorbed in the residuals. In regard to the stochastic noise model, it should be noted that the ARIMA model is not based on the theory of the causes of the patterns in the dependent series. Rather, the task is to describe the nature of the ongoing regularities in the series caused by a number of factors (21).

Some infected foxes collected within the region of first vaccination may have originated from outside this region, but the exact number cannot be determined. However, most of the positive cases detected in the post-vaccination period within the region of first vaccination appeared along the borders of regions which most recently took part in the Slovenian vaccination campaign. The indirect assumption can therefore be made that at least some of the positive cases entered the region after vaccination had been performed. When this factor is taken into consideration, the vaccination appears to be even more successful. In the first six months of 1992, when vaccination had been performed in all regions of Slovenia, no positive cases were recorded within the region of the vaccination.

A closer look at the numbers of fox rabies cases in five communities of the Gorenjska region reveals similarities in the pattern of the disease (Fig. 3). The number of cases in communities 1 and 5 was considerably smaller than in communities 2, 3 and 4, probably due to topographical differences. Communities 1 and 5 are situated at higher altitude (the Alps) and have a lower percentage of agricultural land.

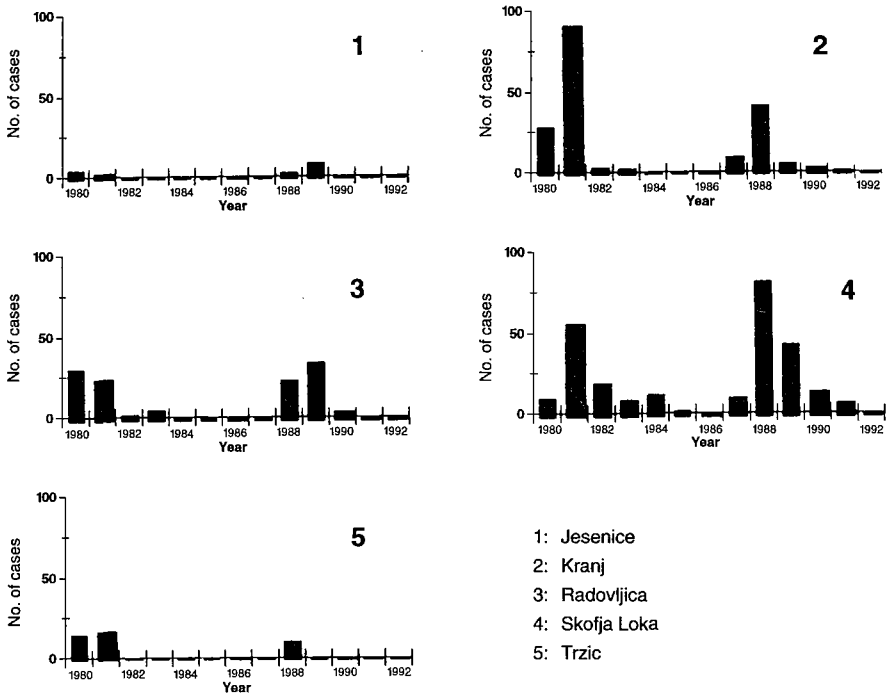


FIG. 3

### Fox rabies occurrence in five communities of the Gorenjska region

Some danger of inaccuracy exists due to the assumption concerning the relation between the dynamics of fox population density and the cyclic patterns of fox rabies outbreaks (7). Firstly, individual differences which affect survival, reproductive and breeding potential could be important mechanisms of population regulation. As rabies is highly lethal for foxes, major selective advantages would favour foxes with increased resistance, decreased chances of contracting the disease, etc. Secondly, the incubation time of rabies may vary greatly. In a population of foxes where contacts are frequent, a virus type with a short incubation period will spread rapidly and will tend to become more common than a type with longer incubation periods. However, in a population of foxes where contacts are infrequent at low density, but population size is increasing, the virus with short incubation period will spread less rapidly, as persistence will depend on the occurrence of several rare contacts per unit of time.

This is not the first time-series analysis of fox rabies control. Other investigators have collected data and performed time-series analyses of vaccination efficacy, although not using the same techniques (31, 35, 40). The use of intervention analysis in assessing the results of the vaccination campaign can overcome some of the shortcomings of cross-sectional approaches. Cross-sectional approaches typically compare the rabies cases in a 'vaccinated' area with the cases in a 'non-vaccinated' area, and the most frequent problem arising in such studies concerns the comparability of the areas studied. In addition, cross-sectional approaches are static, while intervention analysis can take into account the dynamics of population and disease occurrence.



There are limitations to a study of this kind: uncertainty still exists regarding some of the factors which influence rabies occurrence and fox immunisation; and data on some variables are unavailable, which may lead to specification errors.

Also, a certain amount of bias is expected in the data base. Submission rate depends on the price of the tests, the price of fox fur, and the economic situation of hunting organisations (due to the unsolved question of laboratory testing payments). These factors are partially reflected in the percentage of cases detected (Table I).

The next point of concern is whether the time series considered are sufficiently long. It is difficult to say what constitutes 'sufficient length' of a time series. In statistical work, the amount of information in a random sample may usually be considered proportional to the size of the sample. The variance of many of the estimates derived from random samples is inversely proportional to the sample size. However, in time series analysis, successive observations are not independent. The precision of estimates depends on both sample size and the internal structure of the series (25). According to Chambers *et al.* (18) and Wheelwright and Makridakis (42), at least 36 observations per series are required to recognise and handle horizontal, trend, seasonal and cyclical patterns of data, while Montgomery *et al.* (29) state that a minimum of 50 observations are required to produce a satisfactory estimate of the cross-correlation function used to identify transfer function models. In the present study, data from 149 months were examined.

The identification of the noise model may cause problems. Sometimes, the noise model may be identified with observations of the output time series up to the time of the intervention. If intervention effects are likely to be small, or if few observations relate to the post-intervention period compared to the total length of the series, the entire output series can often be used for the noise identification. In situations where the intervention effects are strong and dominate the series, these effects must be treated first. The nature of the intervention effects can be estimated by the *a priori* knowledge of the analyst and by conventional identification procedures (28).

The Student's *t* test is a parametric method which is widely used in testing differences between two means. However, the ordinary *t* test would be valid only if the observations before and after the event of interest varied about the two means not only 'normally' and with constant variance but also independently (15). A formal presentation of the inadequacy of the *t* test in the presence of autocorrelation is provided by Abraham (1). The time series of fox rabies cases in Gorenjska and throughout Slovenia, as well as rates of monthly submissions, were serially correlated. This was one of the reasons for preferring intervention analysis. In the intervention analysis, the stochastic model for the noise ( $N_t$ ) comprised serial correlation in the data such that the residuals were distributed independently.

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## EFFICACITÉ DE LA PREMIÈRE VACCINATION PAR VOIE ORALE CONTRE LA RAGE VULPINE EN SLOVÉNIE. – A. Curk et T.E. Carpenter.

**Résumé :** La lutte contre la rage des renards a consisté, en premier lieu, à réduire leurs populations, mais cette méthode s'est révélée inefficace. Les résultats prometteurs de l'immunisation par voie orale des renards contre la rage dans certains pays européens a incité la Slovénie à autoriser la première vaccination antirabique de cette population sur le terrain en octobre 1988. Dans la présente étude, une analyse d'intervention a permis d'évaluer les résultats de la campagne de vaccination. Cette analyse a tenu compte de la nature cyclique de la rage vulpine et des effets possibles d'un taux variable d'envoi de cadavres de renards pour diagnostic de rage. Les résultats ont confirmé la diminution de la rage vulpine après le lancement de la campagne de vaccination. Cette diminution n'étant pas due aux variations cycliques de la maladie, ni à celles du taux d'envoi de prélèvements pour diagnostic, l'analyse conclut à l'efficacité réelle de la vaccination.

MOTS-CLÉS : Epidémiologie – Rage – Renards – Slovénie – Vaccination.

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## EFICACIA DE LA PRIMERA VACUNACIÓN POR VÍA ORAL CONTRA LA RABIA VULPINA EN ESLOVENIA. – A. Curk y T.E. Carpenter.

**Resumen:** La primera medida que se tomó en la lucha contra la rabia vulpina fue reducir la población de zorros, pero resultó ineficaz. Los resultados en cambio prometedores, en algunos países europeos, de la inmunización de los zorros contra la rabia por vía oral llevó a las autoridades de Eslovenia a permitir una primera campaña de vacunación antirrábica de estos animales en el terreno, en octubre de 1988. Este estudio presenta un análisis de intervención que ha permitido evaluar los resultados de la campaña. El análisis tuvo en cuenta la naturaleza cíclica de la rabia vulpina y los efectos posibles de las variaciones del porcentaje de envíos de los zorros muertos para el diagnóstico postmortem de la enfermedad. Los resultados observados confirmaron la disminución de la rabia vulpina una vez lanzada la campaña de vacunación. En la medida en que esta disminución no pudo atribuirse ni a las variaciones cíclicas de la enfermedad ni a las variaciones del porcentaje de envíos de zorros muertos para diagnóstico postmortem, se pudo concluir que la vacunación había tenido una real eficacia.

PALABRAS CLAVE: Epidemiología – Eslovenia – Rabia – Vacunación – Zorros.

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