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## Rabies oral vaccination of foxes during the summer with the VRG vaccine bait

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**Abstract** – The vaccination of foxes by distributing vaccine baits in the environment was initiated in France in 1986. Two campaigns per year were carried out: one in the spring and one in the autumn. After the spring campaigns, only 22–52 % of fox cubs consumed vaccine baits compared to 75 % of the adults and 70–80 % of the adults or fox cubs after autumn campaigns. In order to reduce the period of time during which fox cubs do not have access to baits and are not immunised, a vaccination campaign was organised during the summer of 1992 over a contaminated area of 25 748 km<sup>2</sup> where vaccines had never previously been given. Vaccine bait stability was assessed during the same summer in the field and their appetence tested on captive foxes. The efficacy of the campaign was evaluated by the relative decrease in rabies incidence and the rate of bait uptake by foxes compared to those from neighbouring areas vaccinated for the first time with the same vaccine during the spring or autumn. Summer vaccination significantly increased ( $P < 0.01$ ) bait uptake by fox cubs (71 %) compared with spring vaccination (39 %), but no significant difference was observed for adult foxes. Moreover, the decrease in rabies incidence, measured during the 6-month period following the campaigns was less pronounced after summer vaccination (49 % decrease) than when the first vaccination was carried out during the spring or autumn (79 and 72 % decrease, respectively). Three campaigns led to an apparent elimination of rabies when the first campaign was performed in the spring or autumn, but only to a 76 % decrease in rabies incidence density index when the first campaign was performed during the summer. The high thermostability of the Raboral VRG bait permits its use during the summer for an emergency campaign. For routine vaccination plans, however, the classical calendar of spring and autumn vaccination campaigns should continue to be preferred. © Inra/Elsevier, Paris.

**rabies / oral immunisation / summer / fox / VRG vaccine**

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**Résumé – Vaccination antirabique du renard en été avec l'appât VRG.** La lutte contre la rage vulpine par distribution d'appâts vaccinaux a débuté en France en 1986. Deux campagnes de vaccination sont réalisées chaque année : une au printemps et une à l'automne. Lors des campagnes de printemps, on estime que seulement 22 à 52 % des renardeaux consomment des appâts contre environ 75 % des adultes, tandis qu'après les campagnes d'automne, 70 à 80 % des jeunes et des adultes auront consommé des appâts. Afin de limiter la période durant laquelle une faible proportion de jeunes est immunisée, des essais de vaccination ont été conduits avec le recombinant vaccine-rage (Raboral VRG) durant l'été 1992 sur une surface de 25 748 km<sup>2</sup> qui n'avait jamais été vaccinée auparavant. La stabilité des appâts-vaccinaux exposés aux conditions estivales a été vérifiée sur le terrain ainsi que leur appétence sur renards captifs. L'efficacité de cette campagne a été mesurée en suivant le taux de prise des appâts et l'incidence de la rage comparés à des zones voisines, vaccinées pour la première fois en automne ou au printemps, avec le même type d'appât. La vaccination d'été a permis d'accroître de façon significative ( $p < 0,01$ ) le taux de prise d'appâts chez les renardeaux (71 %) comparé à celui obtenu au printemps (39 %) mais aucune différence significative n'a été observée chez les adultes. D'autre part, la baisse significative d'incidence de la rage dans les 6 mois suivant la vaccination semble moins marquée après une vaccination d'été (baisse d'incidence : 49 %) qu'après une vaccination de printemps (baisse de 79 %) ou d'automne (baisse de 72 %). Après trois campagnes de vaccination, une élimination apparente de la rage a été obtenue lorsque la première campagne avait été effectuée au printemps ou en automne, alors que l'on a obtenu seulement une diminution de 76 % de l'incidence de la rage lorsque la première campagne avait été effectuée en été. La très bonne stabilité de l'appât Raboral permet donc son utilisation lorsqu'une intervention d'urgence est nécessaire même en condition estivale. Cependant dans le cadre de plans de vaccination habituels, le calendrier classique de vaccination au printemps et à l'automne paraît préférable. © Inra/Elsevier, Paris.

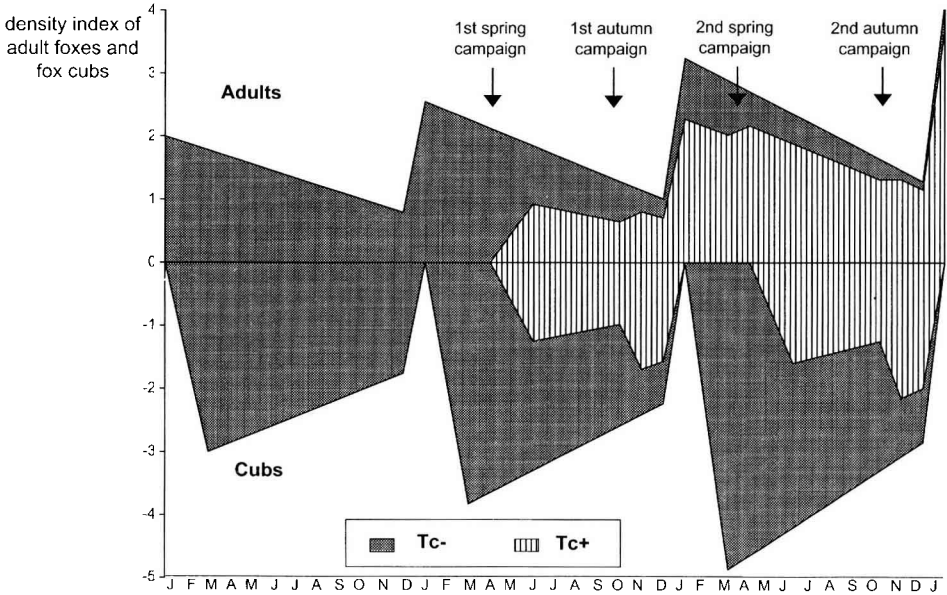
## rage / vaccination orale / été / renard / vaccin VRG

### 1. INTRODUCTION

When initiating the first field trials of oral vaccination of foxes against rabies in Switzerland in 1978, Steck et al. [22] distributed vaccine baits twice a year, in the autumn and in the spring. This choice of seasons was intended to: a) avoid a rapid neutralisation of the vaccine by high temperatures; b) reach adult foxes when their density was at its lowest level (whelping takes place during early spring); and c) reach young foxes when they begin to disperse (autumn). In the following years, all other national teams who organised oral vaccination of foxes in European countries followed the Swiss protocol of carrying out two vaccination campaigns per year in the spring and in the autumn [5] including France which initiated oral vaccination of foxes in 1986.

The success of any vaccination campaign depends on the vaccination coverage. Following the distribution of 13 baits per square

kilometre in France, the percentage of adult foxes that consumed vaccine baits, assessed by tetracycline marks in the teeth of foxes sampled in vaccinated areas, reached mean percentages of 75 and 80 % after spring and autumn campaigns, respectively [17]. The same study, however, revealed that only 22–52% of fox cubs consumed baits after spring campaigns and that higher percentages of marked individuals within the fox cub subpopulation (70–80 %) were obtained only after autumn campaigns (*figure 1*). The vaccination of fox cubs has become a key-point for the success of rabies control for two main reasons. 1) The increase in the fox population, a phenomenon assessed by night counting of foxes conducted by wardens according to a standardised method. After the incidence of rabies is reduced, the fox counting index can be multiplied by 3–5 [3, 4]. 2) The high proportion of fox cubs in the fox population and the difficulty in vaccinating them [6] (*figure 1*). Breitenmoser et al. [9] made several observations that sup-



**Figure 1.** Theoretical diagram describing the variation of the fox population during a 3-year period and the proportion of individuals that had access to vaccine baits (TC+) or did not have access to baits (TC-) following spring and summer campaigns.

port the hypothesis that young foxes play a major role in the persistence of rabies in the Swiss Jura. To vaccinate fox cubs, baits were deposited at fox den entrances during a first trial in Switzerland in 1994. This was carried out in France over the following two years [24, 25]. Another approach for vaccinating a higher proportion of fox cubs was attempted whereby the bait distribution was delayed until the summer months when fox cubs were older and beginning to forage by themselves in the greater vicinity of their den [16]. Considering that the rabies virus is quickly inactivated at high temperatures, however, summer distribution of vaccine baits could not be carried out with a modified rabies virus vaccine but only with the more thermostable VRG vaccine. The thermostability of the VRG vaccine has been

extensively demonstrated in various field conditions [20], and has been considered in France as the main factor explaining why highly significant rabies incidence decreases were more regularly observed with the VRG in comparison with rabies attenuated strains [5, 19].

The present study describes thermostability field trials performed in France during the summer of 1992 using VRG vaccine baits and evaluates the efficacy of a vaccination campaign organised during the same summer period over contaminated areas that had never previously been vaccinated. Bait uptake by foxes and decrease in rabies incidence are compared in these areas and in vaccinated areas according to the classical spring/autumn protocol.

## 2. MATERIALS AND METHODS

### 2.1. Vaccine bait

The vaccinia rabies glycoprotein recombinant vaccine (VRG) was developed by inserting the rabies virus glycoprotein gene from the ERA strain into the thymidine-kinase gene of the vaccinia virus (Copenhagen strain) [14]. The bait was a rigid  $5 \times 3 \times 2$  cm parallelepiped weighing 34–40 g made of a solid envelop of fish flour and fish oil aggregated by a hydrophobic synthetic polymer. In the middle of this parallelepiped, a polyethylene sachet containing 2.5 mL of VRG liquid suspension was sealed with paraffin. The vaccine titre in the baits sampled in the remnant stock after campaigns ranged between  $10^{7.3}$  and  $10^{8.2}$  TCID<sub>50</sub> per millilitre.

### 2.2. Stability trial in the field

This trial was carried out in the laboratory of the experimental farm at Atton (Meurthe-et-Moselle, France). A total of 200 vaccine baits was taken at random from the batch ref. BLV OT 631, delivered to our laboratory by Merial laboratories in May 1992 and stored at 4 °C until use.

On 20 July 1992, 100 baits were ground-deposited at different places either in the open sun, under the moderate shade of an ash plantation – in the middle of 20 cm high grass or on scrapped soil. In order to prevent the removal of baits by birds or mammals, baits were protected with a thin metal mesh (2 × 2 cm). In each place of bait deposit, minimum/maximum thermometers were placed and temperatures were recorded daily. Additionally, data from the meteorological station Météo-France, located 8 km away from the farm were gathered during the entire experimental period. Five baits were sampled in each place at days 3, 7, 14 and 21, and stored at 4 °C until titration of the vaccine suspension on VERO cells. At day 21, baits were given to caged foxes for acceptability tests.

### 2.3. Vaccination campaigns and follow-up

The distribution of baits has been described previously [19]. Regardless of the season, the baits were distributed by helicopters (Ecureuil A5 350 B). Helicopter distribution enables pre-

cise dropping, as it offers optimal visibility of the ground and its flight speed and direction may be modified according to the zone where baits are to be distributed. Helicopters also make it possible to work in less favourable weather conditions. Baits were dropped by a permanent team of ten people trained for the task. Each square kilometre was covered two or three times at an altitude of 60–100 m and an average speed of 180 km/h. The mean density of the droppings was 13 baits per square kilometre; however, baits were preferably dropped over the habitats that were supposed to be the most suitable for foxes and away from human dwellings: hedges, isolated groves, orchards, banks of brooks, limits between meadows, cultivated areas and forests. Four helicopters were able to cover on average 2 500 km<sup>2</sup> per day, and flights were plotted onto a 100 000 scale map. The bait number, surface, flight time, weather conditions and names of those involved were duly noted.

Study areas were located in the north-east of France and the VRG vaccine baits were distributed for the first time during the spring, summer or autumn. The same vaccines were then distributed twice a year until elimination of rabies. These three areas and the periods of the first vaccination campaigns were as follows.

- Area A (*figure 2*): the vaccines were given during the spring of 1990 (15 536 km<sup>2</sup>), 1991 (2 431 km<sup>2</sup>) and 1992 (2 565 km<sup>2</sup> (cumulated area: 20 532 km<sup>2</sup>)). The areas were located in the west of Burgundy and east of Berry, in the southern part of the Vosges mountains and on the Lorraine plateau. In the east of Berry, the treated areas were mainly middle-sized cereal fields and meadows separated by tree hedges and in the west of Burgundy, they were predominantly deciduous forests with patchy cultures.
- Area B: the vaccines were given during the summer (3 August–9 September 1992). During this period the vaccination team recorded maximal diurnal temperatures above 25 °C for 3 weeks. The total size of the area was 25 748 km<sup>2</sup>. It included various milieus (from west to east): the plain of Champagne occupied by open fields and vineyards on slopes, the Lorraine plateau (mean altitude: 300 m) with mixed deciduous forests, cattle farming and open cereal fields, the Vosges mountains (culminating at 1 424 m) mainly covered by conifer and deciduous forests and meadows, and an Alsace plain occupied by open cultures, the Hardt forest and on the slopes, by vineyards.



**Figure 2.** Areas vaccinated for the first time with the Raboral VRG bait during the spring (A), summer (B) or autumn (C).

- Area C: the vaccines were given during the autumn of 1990 (1 960 km<sup>2</sup>) and autumn of 1991 (1 639 km<sup>2</sup> cumulated area; 3 599 km<sup>2</sup>). This area was located near the previous ones in the Berry and Burgundy provinces.

Rabies cases were followed as described by Barrat and Aubert [7]. For all vaccinated areas, the total number of diagnosed rabies cases (all species included) was determined over a 6-month period following each campaign. Since the incidence of rabies and its dynamics before any vaccination campaign were of critical interest for judging the success of the treatment, the number of rabies cases during the two 6-month periods preceding any vaccination bait distribution (1–6 months and 7–12 months before vaccination) were recorded. Because rabies incidence follows seasonal variations (review in Aubert [2]), the variation of rabies incidence following vaccination may be a combination of the seasonal effect and treatment efficacy. In order to eliminate the possible source of bias introduced by natural seasonal variation of rabies incidence, rabies case densities recorded during the 6 months following the first vaccination cam-

paigns performed during the spring, summer or autumn, were compared with rabies case densities recorded in the same areas during the same 6-month period of the previous year. These latter densities were taken as the 100 indexes.

Tetracycline, a biological marker (150 mg per bait), was searched for in the lower jaw and inferior canine of a total of 634 foxes sampled in the vaccinated zones between the 2nd and the 6th month after the end of the vaccination campaigns. Tetracycline was detected by ultraviolet light examination of a section of the canine by inverse microscopy (model IMT 2-RFL, Olympus). Longitudinal sections of canines and lower jaws (thickness 500–700 µm) were prepared with a diamond circular saw (model Buehler-isomet<sup>nd</sup>). Tetracycline deposits appeared as pale yellow on a blue background [12]. According to Kappeler [13] and Masson [17] bait uptake must be studied in fox cubs (i.e. foxes less than 12 months of age) and adult foxes separately; therefore, we differentiated both age categories on the basis of histological dental examination as proposed by Johnston and Watt [11].

### 3. RESULTS

#### 3.1. Thermostability field trial

The maximum and minimum temperatures recorded on the ground near the baits and the environmental temperatures (meteorological records) are described in *figure 3*. Extreme temperatures near the baits on the barren ground ranged between 5 and 16 °C during the night and between 44 and 57 °C during the day. The mean daily variations of local temperature were 41 °C (range: 36–46 °C) for baits exposed in the open sun on a barren ground and 32 °C (range: 23–37 °C) for baits deposited in the grass under tree shade. During the same period, meteorological records indicated extreme air temperatures between 8 and 21 °C during the night and between 24 and 37 °C during the day (mean daily variation: 17 °C – range: 8–24 °C). It did not rain during the experiment.

The baits did not melt and the only changes observed were that the surface of the baits became less smooth and the lat-

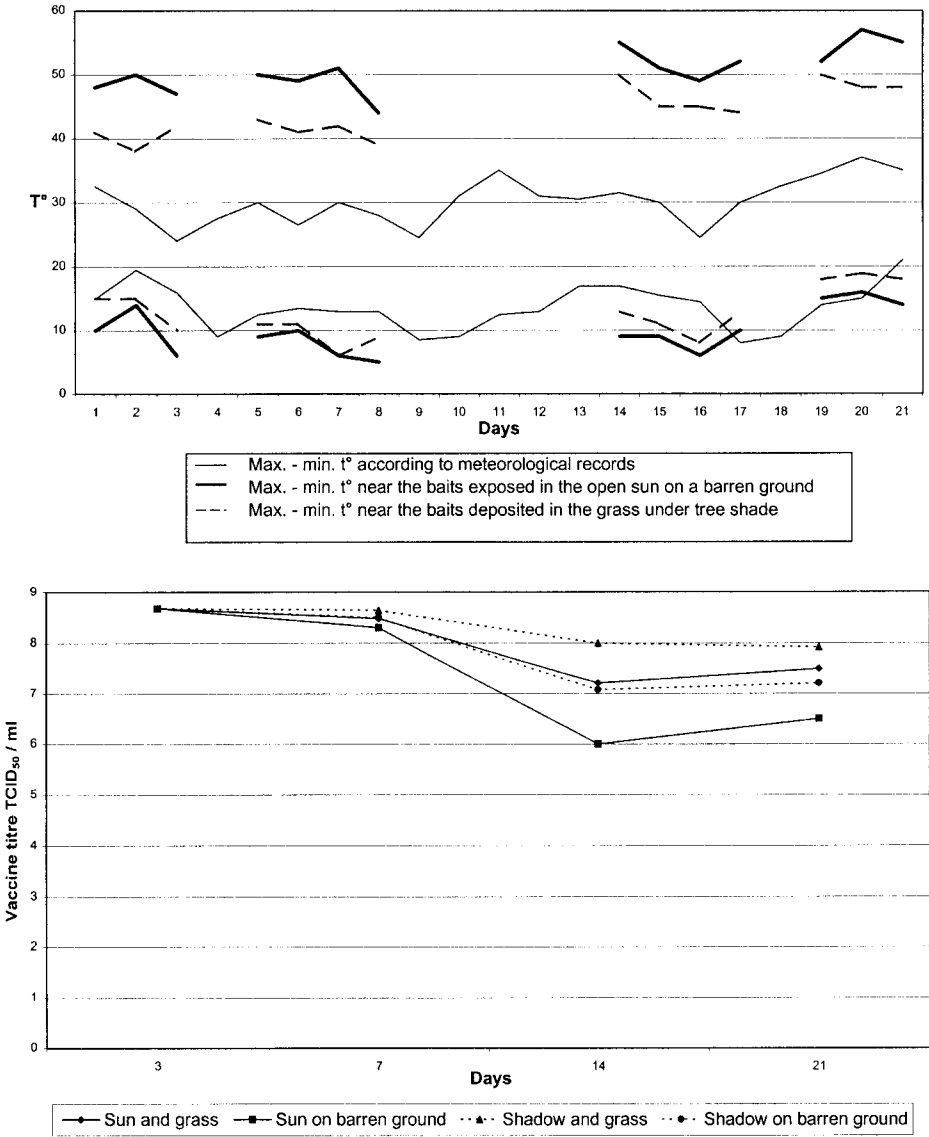


Figure 3. Stability trials of the Raboral VRG vaccine bait in summer conditions.

eral paraffin seals became soft during the hottest hours of the day but hardened back in the middle of the afternoon. Even though high temperatures provoked a small loss of paraffin, the central canal of the bait was

never forced open and the vaccine sachet was never released or even partly disclosed.

Ten baits were sampled at random after 21 days from those deposited on the barren ground in the open sun, and were distributed

to five caged foxes (two baits per fox). Even though they had received their usual daily food intake, the foxes rapidly consumed the baits.

The vaccine titre of the baits is described in *figure 3*. After 21 days in shaded grass, the decrease in titre was  $10^{0.8}$  TCID<sub>50</sub>/mL and in the open sun it was  $10^{2.2}$  TCID<sub>50</sub>/mL.

### 3.2. Summer vaccination campaigns using VRG

#### 3.2.1. Rabies incidence

Compared with the rabies incidence that prevailed during the 6-month periods 1 year

before the vaccination treatment, the rabies incidence densities decreased by 79, 49 and 72 % when this first treatment was carried out in the spring, summer and autumn, respectively (*table 1*).

Following these first vaccination campaigns, two more campaigns were performed following the usual spring/autumn protocol. They led to an apparent elimination of rabies when the first campaign was performed in the spring or autumn, but only to a 76 % decrease in rabies incidence density index when the first campaign was performed during the summer. Furthermore, in the latter case, rabies was not eliminated even after four campaigns.

**Table 1.** Rabies cases and incidence in areas treated with the VRG vaccine bait.

	Periods of 6 months					
	Before the first campaign			After campaigns		
	-2	-1	1st	2nd	3rd	4th
<i>First campaign in spring</i>						
Cumulated area (km <sup>2</sup> )	20 532	20 532	20 532	20 293	19 730	10 668
Rabies cases (number)	377	516	79	4	0	0
Density (number/100 km <sup>2</sup> )	1.84	2.51	0.38	0.02	0	0
Relative rabies incidence index						
Series 1	100		21		0	
Series 2		100		0.8		0
<i>First campaign in summer</i>						
Cumulated area (km <sup>2</sup> )	25 748	25 748	25 748	24 940	24 940	22 271
Rabies cases (number)	423	245	216	70	51	17
Density (number/100 km <sup>2</sup> )	1.64	0.95	0.84	0.28	0.2	0.07
Relative rabies incidence index						
Series 1	100		51		24	
Series 2		100		29		7
<i>First campaign in autumn</i>						
Cumulated area (km <sup>2</sup> )	3 599	3 599	3 599	2 794	1 155	1 155
Rabies cases (number)	22	11	6	2	0	0
Density (number/100 km <sup>2</sup> )	0.61	0.31	0.17	0.07	0	0
Relative rabies incidence index						
Series 1	100		28		0	
Series 2		100		23		0

Comparison between areas vaccinated for the first time in the spring, summer or autumn.

The relative rabies incidence indexes are taken as 100 before vaccination campaigns for the 6-month periods 1 year before the corresponding 6-month periods that followed the vaccination campaigns. This method of calculation produces two embedded series of related indexes.



### 3.2.2. Bait uptake

Bait uptake was evaluated by the examination of foxes sampled for tetracycline after the first vaccination campaigns (*table II*). The percentage of fox cubs who were tetracycline positive was significantly ( $P < 0.001$ ) lower (39 %) when the first campaign was performed in the spring than after a first campaign in the summer or autumn (71 or 74 %). The percentage of adult foxes who were tetracycline positive was significantly lower ( $P = 0.02$ ) after a first vaccination in the spring (50 %) or in the summer (56 %) than after a first vaccination in the autumn (76 %).

## 4. DISCUSSION

### 4.1. Stability of VRG baits during the summer

After 3 weeks under natural field conditions during the summer, and despite exposure to temperatures as high as 57 °C and natural thermal cycles with daily variations as large as 46 °C, the loss in titre of the vaccine was 1.4 log units at most, and the lowest titre measured in the baits was  $10^7$  TCID<sub>50</sub>/mL. This lowest limit is still considered to be sufficient to protect foxes against a severe challenge with a homologous rabies virus strain [8]. Since this trial was performed, other authors [20] have demonstrated that several natural freezing and thawing cycles in the spring do not alter

the titre of the VRG vaccine, confirming the good field stability of this vaccine under any meteorological condition. Additionally, despite the hot conditions during the study, the bait casing remained hard enough to maintain its shape and consistency and to keep the vaccine sachet well enclosed. Moreover, the baits did not lose their attractiveness for well-fed captive foxes.

The stability results obtained in this trial confirmed that the titre of the VRG baits that we measured on several samples just prior to helicopter flights were not significantly altered by meteorological factors after dropping. Other factors contributed to providing foxes with high titre vaccines:

- when deposited, most of the baits, including those which were well hidden in the vegetation, were consumed within 2 weeks [21];
- technicians that dropped the baits from the helicopters were trained to avoid barren earth surfaces such as trails and ploughed fields. The use of helicopters allowed a precise dropping of vaccines into the vegetation. The first advantage of this was to place the baits in a buffered micro-climate. Other advantages were to prevent large birds from consuming the baits: scavenger species such as kites have been shown to take baits deposited in open view [21]. It is also important to avoid depositing baits along the trails where they are regularly picked up by domestic dogs [18].

**Table II.** Tetracycline examination in adult foxes and in fox cubs in areas treated with the VRG vaccine bait. Comparison between areas vaccinated for the first time in the spring, summer or autumn.

First vaccination campaigns :	Spring	Summer	Autumn
Fox cubs	14/36 (39) <sup>a</sup>	50/70 (71)	29/39 (74)
Adult foxes	10/20 (50)	54/96 (56)	31/41 (76)

<sup>a</sup> Number (%) of foxes positive for tetracycline/total examined.

#### **4.2. Comparison of the efficiency of bait distribution during the spring, summer or autumn**

The efficiency of bait distribution was evaluated using two parameters: bait uptake by foxes and the decrease in rabies incidence in the vaccinated areas.

##### **4.2.1. Bait uptake by foxes**

This study confirmed the observations made in Switzerland by Kappeler [13] who described similar percentages of tetracycline-positive foxes after early campaigns: more fox cubs and adults consumed baits after a first campaign in the autumn than after one in the spring. During the spring campaign, most of the fox cubs had a limited access to the baits, even when adult foxes carried baits to the dens [25]. Only when fox cubs forage at a certain distance from the den do they have a direct access to the baits distributed by helicopter: this was the case during the summer or autumn with no difference in this respect between either season.

More adults are marked by tetracycline after a first campaign in the autumn than one in the spring or summer. As already stated by Kappeler [13], there is no satisfactory hypothesis that explains this difference: because less food resources are available in the spring than during the autumn, baits should be more readily consumed by adult foxes during the spring. An explanation may be found in the seasonal variation of fox activity. According to Tembrock [23] and Hilmer et al. [10], captive foxes are more active during the autumn than during the spring. This tendency has been confirmed on free-ranging foxes by Kolb [15] who followed 15 foxes by radiotracking and observed the smallest ranges in late spring and summer. Weber et al. [27] measured longer activity periods in the autumn than in the spring for four out of five foxes. This higher activity in the autumn compared with the spring may lead foxes to more intensely

explore their activity area and to find baits more often.

##### **4.2.2. Rabies incidence**

Following a first campaign in the spring, the proportion of foxes marked with tetracycline was at its lowest, whereas this campaign produced a 79 % decrease in rabies incidence. First campaigns in the summer or in the autumn entailed an equal proportion of marked foxes, but produced a 49 and 72 % decrease in rabies incidence, respectively. Obviously, the decrease in rabies incidence is not only dependent on the percentage of foxes that have consumed baits, but is also due to other parameters such as fox behaviour, which varies according to the seasons. During the spring and early summer, fox activity is not the most favourable to rabies transmission: adults are not at their peak activity and the movements of cubs are restricted to the vicinity of the den [26]. A medium vaccination coverage may be sufficient to avoid the infrequent inter-individual contamination. When the dispersal of fox cubs begins (in September according to Lloyd [16]), rabies incidence may have already been decreased. On the contrary, vaccination in the summer, despite offering a high access to baits, may not allow the necessary delay for fox cubs to develop a protective immunity before dispersal.

The proportion of foxes that had eaten baits was the highest after a first campaign in the autumn. There was also a significant decrease in rabies incidence.

#### **4.3. Relevance of summer campaigns**

As discussed in a previous paper [19], the management of fox sampling for the evaluation of bait uptake and the organisation of bait distribution by the same team contribute to the consistency of the experimental approach. Moreover, despite the uncontrolled bias of fox sampling for rabies surveillance, it has already been discussed

that the perspective of rabies elimination aroused the motivation of the general public, of the veterinary practitioners and of local veterinarian authorities for intensifying the epidemiosurveillance. Rabies epidemics remain, however, a stochastic process not only influenced by vaccination. Many non-controlled factors modulate the driving forces of the disease as illustrated by mathematical modelling [1]. This requires careful conclusions on field data. Nevertheless, the first campaign that we organised during the summer allowed a significant increase in bait uptake by fox cubs as hypothesised, but proved to be less efficient for decreasing rabies incidence than campaigns carried out in the spring or autumn. This relative lack of efficiency of the summer campaign cannot be explained by the thermostability of the vaccine or the bait envelope. The field experiment organised during the same period demonstrated the very high stability of the Raboral VRG vaccine bait.

Therefore, when disease appears in a non-infected area with a high density of foxes, the rapid spreading of the disease may be prevented with an immediate intervention whatever the season, using highly thermostable baits, such as the Raboral VRG vaccine bait. At least two additional campaigns, according to the usual calendar, must thereafter be carried out. For the initiation of a vaccination programme, however, a first campaign in the spring or autumn is necessary.

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