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The spatio-temporal dynamics of a post-vaccination resurgence of rabies in foxes and emergency vaccination planning

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Abstract

We used a simulation model to study the spatio-temporal dynamics of a potential rabies outbreak in an immunized fox population after the termination of a long-term, large-scale vaccination program with two campaigns per year one in spring and one in autumn. The 'worst-case' scenario of rabies resurgence occurs if rabies has persisted at a low prevalence despite control and has remained undetected by a customary surveillance program or if infected individuals invade to the control area. Even if the termination of a vaccination program entails such a risk of a subsequent new outbreak, prolonged vaccination of a wild host population is expensive and the declining cost-benefit ratio over time eventually makes it uneconomic. Based on the knowledge of the spatio-temporal dynamics of a potential new outbreak gained from our modelling study, we suggest ''terminating but observing'' to be an appropriate strategy. Simulating the decline of population immunity without revaccination, we found that a new outbreak of rabies should be detected by customary surveillance programs within two years after the termination of the control. The time until detection does not depend on whether vaccination was terminated within the fourth, fifth or sixth years of repeated biannual campaigns. But it is faster if the program was completed with an autumn campaign (because next-year dispersal then occurs after a noticeable decrease in population immunity). Finally, if a rabid fox is detected after terminating vaccination, we determine a rule for defining a circular hazard area based on the simulated spatial spread of rabies. The radius of this

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area should be increased with the time since the last vaccination campaign. The trade-off between the number of foxes potentially missed by the emergency treatment and the cost for the emergency measures in an enlarged hazard area was found.

Keywords: Fox; Rabies virus; Immunization; Control planning; Emergency vaccination

1. Introduction

Rabies is an infectious, zoonotic disease whose lethality for humans necessitates world-wide efforts to combat it (Charlton, 1988). In Europe, rabies occurs in a sylvatic cycle. The red fox (*Vulpes vulpes*) is the main vector and the major host (Wandeler et al., 1974). Sylvatic rabies entered the European fox population in the mid-20th century, spreading from the east throughout the whole continent (Macdonald and Voigt, 1985; Steck and Wandeler, 1980). Despite various management policies in rabies control, the first notable results were only achieved by the use of oral vaccination in the main vector (Steck et al., 1978; Winkler and Bögel, 1992; Stöhr and Meslin, 1996).

Long-term, large-scale oral vaccination such as that applied in Europe (Barrat and Aubert, 1993; Schlüter and Müller, 1995; Masson et al., 1996) continuously immunized on average 70% of the fox population (Schmid, 1986; Brochier et al., 1988; Barrat and Aubert, 1993), resulting in a drastic decrease of rabies incidence (Stöhr et al., 1994). Consequently, rabies has not been detected for several years in large areas — which suggests the successful regional eradication of the disease (Schlüter and Müller, 1995). However, ongoing surveillance programs have discovered isolated rabies cases within vaccination areas (Schlüter et al., 1997; Müller, 1998). We performed a simulation study to understand the phenomenon (Tischendorf et al., 1998) and found the low-level persistence of rabies linked to the vaccination of foxes (i.e. additionally to the classical concepts of resurgence and eradication; see Section 3.1). In particular, sporadic isolated case detection might indicate low-level persisting rabies or, in the 'worst case,' the customary surveillance may fail to detect the on-going persistence of the disease (Thulke et al., 1997a). Therefore, field data (which include additional detection uncertainty (Bacon, 1981; Schlüter and Müller, 1995)) cannot verify the ultimate success of vaccination programs (i.e. the eradication of the disease).

The uncertainty surrounding final success begs the question of how rabies should be managed after an intensive vaccination program. So far, two alternative strategies have been discussed: prolonged exhaustive vaccination (which would reduce the public-health risk but be very costly) or terminating vaccination while retaining a well-designed, cheaper emergency program to deal with local post-vaccination outbreaks (and, obviously, with any potentially infected foxes immigrating into the post-vaccination area).

The latter strategy requires knowledge of the temporal and spatial dynamics of the rabies outbreak following a finalized vaccination program to determine hazard management. In this paper, we therefore use a simulation model to answer the following questions (see e.g. Stöhr and Meslin, 1996): (1) when is the best time to stop a long-term, large-scale vaccination program? (2) How long after the last vaccination is a new rabies outbreak likely to be detected by usual surveillance? (3) What size area needs to be

vaccinated by an emergency treatment and how does it depend on the time since the last regular vaccination?

2. Model

The study is based on a tested spatial simulation model of the fox–rabies system (Thulke et al., 1999). The stochastic, grid-based model was originally designed to examine the formation of the wavy spatial pattern of rabies spread (Jeltsch et al., 1997), and was also applied to investigate the changed spread of the disease within an immunized host population (Tischendorf et al., 1998). The main features of the model are outlined below (for more details see Jeltsch et al., 1997; Tischendorf et al., 1998; Thulke et al., 1999).

2.1. Temporal resolution and model schedule

The model schedule is oriented to the regular seasonal rhythm of European red foxes (Toma and Andral, 1977). The year is partitioned into six two-monthly steps. The steps relate to the mating season (January–February), the birth event (March–April), the period of parental care (May–June and July–August), the dispersal phase (September–October) and finally the resettlement (November–December; see Thulke et al., 1999 for details).

2.2. Infection communities as basic units

The modelling approach is based on a disease-related breakdown of the fox population and avoids dealing with uncertainties about the fox's life on the individual scale (Macdonald and Bacon, 1982; Thulke et al., 1997b). In particular, we follow the course of the disease in small temporary fox communities (Zimen, 1980; Niewold, 1980; Baker et al., 1998), in which contact rates can be assumed to be high enough to spread a potential infection throughout the whole group immediately (White et al., 1995; White et al., 1996). For the purpose of our model, the members of the group are aggregated into an infection community (IFC).

2.3. Representation of the disease

Each IFC is represented spatially by a cell within a stationary two-dimensional grid. The grid provides the spatial arrangement of IFCs and defines neighborhood relationships between two or more IFCs. The temporal change of an IFC is expressed by a set of possible states. These are SUSCEPTIBLE, if all members are susceptible to an infection; INFECTED, if at least one animal is infected; and EMPTY, for extinct IFCs due to disease mortality. Under vaccination, three further states become possible representing the partial immunization of an IFC, i.e. one portion of the IFC becomes immunized whereas the other part remains either SUSCEPTIBLE, INFECTED or EMPTY (e.g. the resulting state of an SUSCEPTIBLE IFC under vaccination is assigned by SUSCEPTIBLE + IMMUNE).

2.4. Modelling the disease spread

The spread of the disease is modelled by updating the state of each IFC every time step (two months). The new state is determined by the former state of the IFC and the states of its neighbors on the grid. The three transition rules for updating IFCs ('neighborhood infection'; 'mating'; 'dispersal') are related to the biology of fox behavior: (1) infection from the 'neighborhood' of any IFC refers to a potential virus transmission between contacting foxes from adjacent groups throughout the year. (2) Extended neighborhood infection additionally involving IFCs located two or three cells apart around the focal IFC is attributed to itinerant adults during the 'mating' season in winter. (3) Finally, we observe long-distance infection during 'dispersal' (autumn) by an individual-based module for the movement of cubs which potentially carry the disease.

2.5. Parameters

The model uses five adjustable parameters that are relevant in this context (Table 1): three parameters defining the infection probabilities (i.e. SUSCEPTIBLE→INFECTED) within the transition rules ($P_{SI\langle neigh\rangle}$, $P_{SI\langle mat\rangle}$, $P_{SI\langle disp\rangle}$), one probability for whether an infected IFC becomes extinct or survives until the next time-step (P_{IE}), and the parameter IR. IR relates to the immunization coverage estimated for populations from field samples as the mean proportion of all investigated individuals that show immunization signs (e.g. marker or antibodies (Winkler and Bögel, 1992; Stöhr et al., 1994)). For each single simulation run, the parameters for the infection probabilities (i.e. $P_{SI\langle ...\rangle}$ and P_{IE}) define binomial distributions from which a random selection is drawn to determine if an infection event occurs (for example, if there are k INFECTED neighbors around a SUSCEPTIBLE IFC, an infection occurs with probability: $1-(1-P_{SI\langle neigh\rangle})^k$; see Tischendorf et al., 1998 for details). Combinations of different parameter values express different set-ups of epidemiological and biological conditions.

Table 1
Definitions of model parameters and values systematically considered as simulation input for the spatial fox–rabies model (incremental step-size in parentheses)

Parameter	Meaning	Range
$P_{SI\langle neigh\rangle}$	Transition probability SUSCEPTIBLE→INFECTED due to one adjacent IFC within one time-step ('neighborhood infection')	0.24–0.4[a] (0.02)
$P_{SI\langle mat\rangle}$	Transition probability SUSCEPTIBLE→INFECTED due to IFCs which are located within the three rings around the susceptible IFC ('mating')	0.4–0.5[a] (0.1)
$P_{SI\langle disp\rangle}$	Transition probability SUSCEPTIBLE→INFECTED due to an infected individual cub after settling down ('dispersal')	1.0[a]
P_{IE}	Transition probability INFECTED→ EMPTY within one time-step (lethality of rabies)	0.65–0.8 (0.05)
IR	Immunization coverage in percentage[b]	60–80 (2)

[a] Without vaccination, if IR is non-zero the respective values are diminished linearly with IR (see Section 2.6).

[b] The value is determined initially to each simulation run and then diminished progressively following the estimated step-function (see Fig. 1).

2.6. Vaccination

The event 'vaccination' occurs twice a year simulating the baiting campaigns in the field (Barrat and Aubert, 1993). The event is scheduled in the second (March–April) and fifth time-step (September–October). In accordance, all SUSCEPTIBLE IFCs become SUSCEPTIBLE + IMMUNE. In such 'partially immunized' IFCs, the actual proportion of immune animals is assumed equal to IR (see Table 1). Consequently, for transitions involving 'partially immunized' IFCs, the probabilities for the three disease-transmission rules are diminished linearly with IR (e.g. the probability of 'neighborhood' infections under vaccination is determined by $P_{\mathrm{SI}\langle\mathrm{neigh}\rangle} \times (1 - \mathrm{IR}/100)$; see Tischendorf et al., 1998 for details).

2.7. Termination of vaccination

If vaccination is terminated, the mean immunization coverage will decline due to population turnover, i.e. immunized foxes eventually die out. In the spatial rabies model, this is represented by the time-dependent reduction of the value for parameter IR. We estimated the time-dependent reduction of the mean immunization coverage in the fox population as a function of a changing age-structure over time using a Leslie-matrix (see Section 3.4.). The relationship obtained from the matrix-model (Fig. 1a) was approximated by a step-function (Fig. 1b) to reduce the value of the parameter IR in the spatial rabies model. After six time steps (i.e. one year), the actual value of IR is always diminished by 35% (following Fig. 1b). The decline of IR is scheduled in the third time-step of the model (May–June) when the annual offspring definitely leave the den and therefore cubs could be infected from outside the parental group. As a consequence of each IR reduction, the probabilities of infection (by 'neighborhood infection', 'mating' and 'dispersal') increase for the 'partially immunized' IFCs. Six years after the final vaccination, the parameter IR is set to zero because the last immunized fox is assumed to be dead.

3. Methods

3.1. Parameter configurations

Meaningful ranges of parameter values were previously identified by adjusting the model to empirical data of the cyclic and wavy spread of rabies across Europe (see Jeltsch et al., 1997). Data from recent field studies were used to define dispersal distances (Goretzki et al., 1997) and the number of dispersing individuals (Goretzki, 1996 pers. comm.). Each combination of values of our parameters (see Table 1) produced a specific dynamic of rabies classified by the respective outcome of the simulated control program. However, not all of the resulting dynamics fit to the posed questions due to the following arguments. If rabies incidence were increased despite control, case detection would continue and no termination would be attempted. If rabies were eradicated by the simulated control, no post-vaccination outbreak could be investigated. Consequently, it is

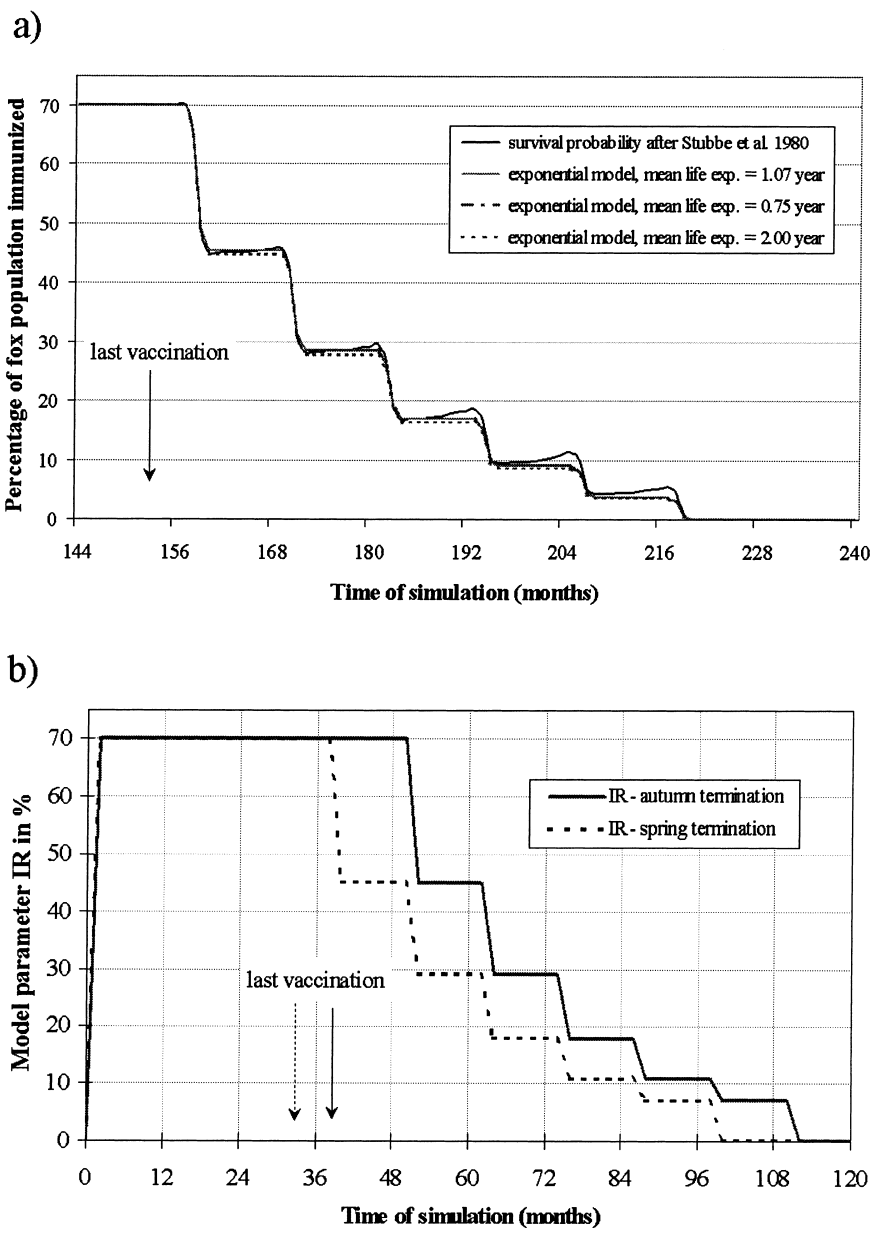

Fig. 1. (a) Decrease in immunization coverage estimated by an age-structured Leslie-matrix model (see Selhorst and Müller, 1999) for different mean life-expectancy assumed for foxes. For each simulation (i.e. value of mean life-expectancy) 144 monthly iterations were performed to reach the stationary age-distribution; (b) approximation of Fig. 1a by a six-valued step function as implemented in the spatial simulation model. The first value of the step function in the graph equals the initial value of the model parameter IR. In the example it was set to 70% but had been varied in the range of 60–80% for different simulation runs. The step function is set to zero after 6 years.

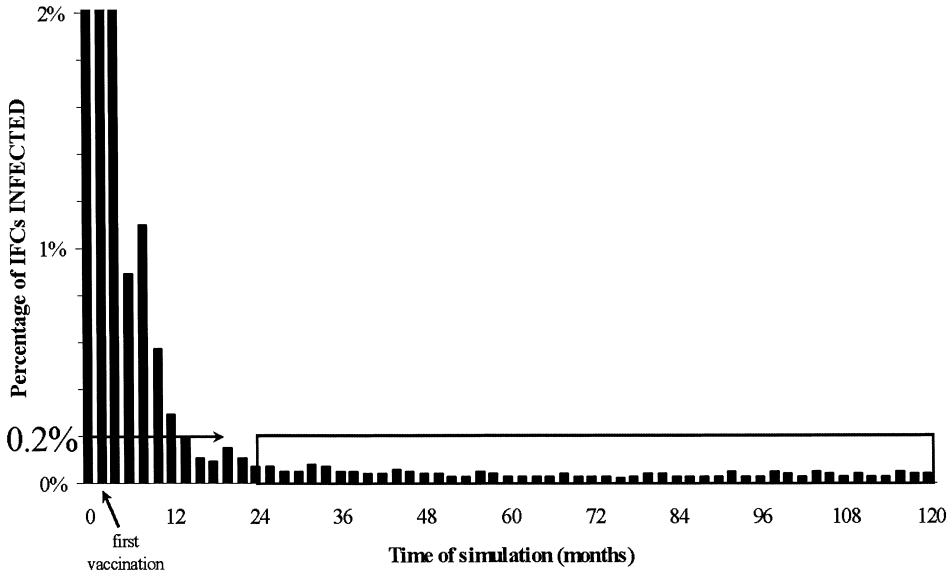

Fig. 2. The definition of low-level persistence of rabies states that from the beginning of the third year of repeated vaccination, the overall proportion of fox groups infected within a simulation area (black columns) is less then 0.2% and is not approaching zero until the end of simulation (solid rectangle in case of a 10-year simulation with vaccination).

most appropriate to investigate the post-vaccination dynamic of rabies if the disease has persisted despite control (i.e. no eradication) but with so few actual cases that it can barely be detected (i.e. no resurgence). This scenario corresponds to the low-level persistence of rabies (Fig. 2) where small variable foci are established within the control area and the disease was not eradicated despite long-term vaccination (Thulke et al., 1997b). In addition, a post-vaccination outbreak can be attributed to invading infected foxes, which at most establish small foci of infection too. All in all, the investigations in this paper are restricted to parameter configurations which produce a low-level persistence of rabies (i.e. small foci of infection).

3.2. Simulation protocol

The spread of rabies was simulated for each of the selected parameter configurations (i.e. which produced low-level persistence). Simulations were performed on a grid of 140×140 cells (because of technical limitations) over 60 time steps (i.e. 10 years composed of 5 years for validation with field data and 5 years of projection) with 100 repetitions for each parameter configuration keeping the respective parameter values constant (i.e. less then 5% standard error for mean number of IFCs INFECTED). Each simulation run was started with an identical spatial set-up of IFC states obtained by simulating uncontrolled rabies spread for 10 years. The total number of available grid cells (i.e. IFCs) did not alter during the whole study. Mimicking the biannually campaigns in the field (Stöhr and Meslin, 1996), vaccination was scheduled at the beginning of the

Table 2
Temporal scenarios for termination of the simulated vaccination program in the spatial rabies model

Termination		Campaigns performed	Season of last campaign	Running month of the simulation when event 'vaccination' is firstly omitted (last performed)
Year	Season			
In fourth year	Spring	6	Autumn third year	38 (32)
	Autumn	7	Spring fourth year	44 (38)
In fifth year	Spring	8	Autumn fourth year	50 (44)
	Autumn	9	Spring fifth year[a]	56 (50)[a]
In sixth year	Spring	10	Autumn fifth year	62 (56)
	Autumn	11	Spring sixth year	68 (62)

[a] Termination scenario behind Fig. 4.

simulation runs (second time-step) and repeated every third time-step (i.e. every 6 months). Six different scenarios of vaccination termination were tested systematically: termination in the fourth, fifth and sixth year of repeated vaccination, with the last vaccination in spring or autumn (see Table 2).

3.3. Spreading distance distribution

Rabies cases within a large, previously vaccinated area are likely to be caused either by foxes immigrating from an adjacent non-vaccinated area (Bacon and Macdonald, 1980; Steck et al., 1982; Barrat and Aubert, 1993; Brochier et al., 1995) or by the low-level persistence of rabies (Tischendorf et al., 1998). In both situations, however, a new outbreak of the disease starts with a small focus of a few infected individuals. Consequently, immediately after the termination of vaccination, neighborhood infections are rare and locally restricted. On the other hand, cubs during dispersal starting from the rare infected IFCs are potential carriers of the infection (i.e. in the incubation period). But then, the cubs might cover a dispersal distance which easily exceeds the extent of the neighborhood disease spread throughout the remaining year (Jensen, 1973; Lloyd et al., 1976; Trewhella et al., 1988). Therefore, close after the vaccination program, the corresponding number of dispersal phases approximately determines (by adding up the maximum distances) the spatial spread of the new outbreak from the originating focus (see results of Garnerin et al., 1986). We imitated four dispersing generations (i.e. one fox and one representative of its descendants from three consecutive offspring generations) by a simulation experiment. The simulation was repeated 2000 times (i.e. 8000 dispersal events, to cover the tail of the resulting distribution). For each of the 2000 simulations, the four straight-line distances between the respective start- and end-points were recorded (i.e. adding up over two, three or four generations). Each individual starts in a random direction at the end-point of the preceding dispersal event and covers a distance randomly drawn from an empirical distribution of dispersal distances of red foxes (i.e. capture–recapture data, Goretzki et al., 1997). As is known from empirical data, there is no evidence of genetic predetermination in either dispersal distance or dispersal direction (Storm and Montgomery, 1975; Woollard and Harris, 1990). We therefore regard two

successive dispersal events as independent from each other and choose the direction and final distance randomly. In the end, the spreading-distance distribution after one, two, three or four consecutive dispersal events (i.e. generations) was derived by summarizing the respective distance records of the 2000 single simulation trials.

3.4. Temporal reduction of immunization coverage in a hunted fox population

The factors changing the mean proportion of immunized foxes over time are governed by reproduction, hunting and life-expectancy. Starting from an immunization coverage established within the vaccinated fox population, the decrease in immunization was determined from the proportion of immunized animals that suffer from mortality and are substituted by non-immune animals from the next offspring generation. Substitution was simulated with an age-structured Leslie-matrix model (Leslie, 1945; Selhorst and Müller, 1999). IMMUNE animals were shifted forward through the age classes relative to the turnover of the fox population and eventually die. Input for simulations was provided by the distributions for reproduction and hunting mortality taken from field data for red foxes (Storm et al., 1976; Stubbe, 1980). Due to the lack of reliable field data concerning the mean life-expectancy of non-hunted red foxes, different simulations were performed varying natural mortality (Fig. 1a). The parameter life-expectancy was tested throughout the range of 0.75 to 2 years. The investigated range for mean life-expectancy excludes both non-natural scenarios: the fox population snowballing to infinity or dying out. For each value of life-expectancy, the temporal decrease of mean immunization in the fox population no-longer being vaccinated was simulated. The simulated relationship for the decrease of immunization coverage over time was found to be insensitive to varying mean life expectancy (see Fig. 1a). The estimated relationship (Fig. 1a) shows a step-like decrease always in spring when the birth of a new generation occurs. The values found for each step form a geometric sequence independent of the life expectancy assumed. Therefore, the nearly 35% decrease in each step was implemented in the spatial rabies model by a six-valued step function decreasing annually the initial immunisation coverage (Fig. 1b).

4. Results

4.1. Temporal aspects

For each parameter configuration (i.e. over 100 repetitions), we investigated the time series of infected IFCs from the six different termination scenarios (i.e. after 3, 4 and 5 years of biannual vaccination in spring and autumn, respectively). We found equivalent baseline dynamics and noticeable differences in the amplitudes of the time-series between different parameter configurations. Referring to the general equivalencies found between the parameter configurations, we derive the answer to the first question (i.e. concerning the best point in time for termination) from the comparison of the six termination scenarios for each parameter configuration (for visualization, Fig. 3 depicts the six scenarios for one configuration arbitrarily chosen).

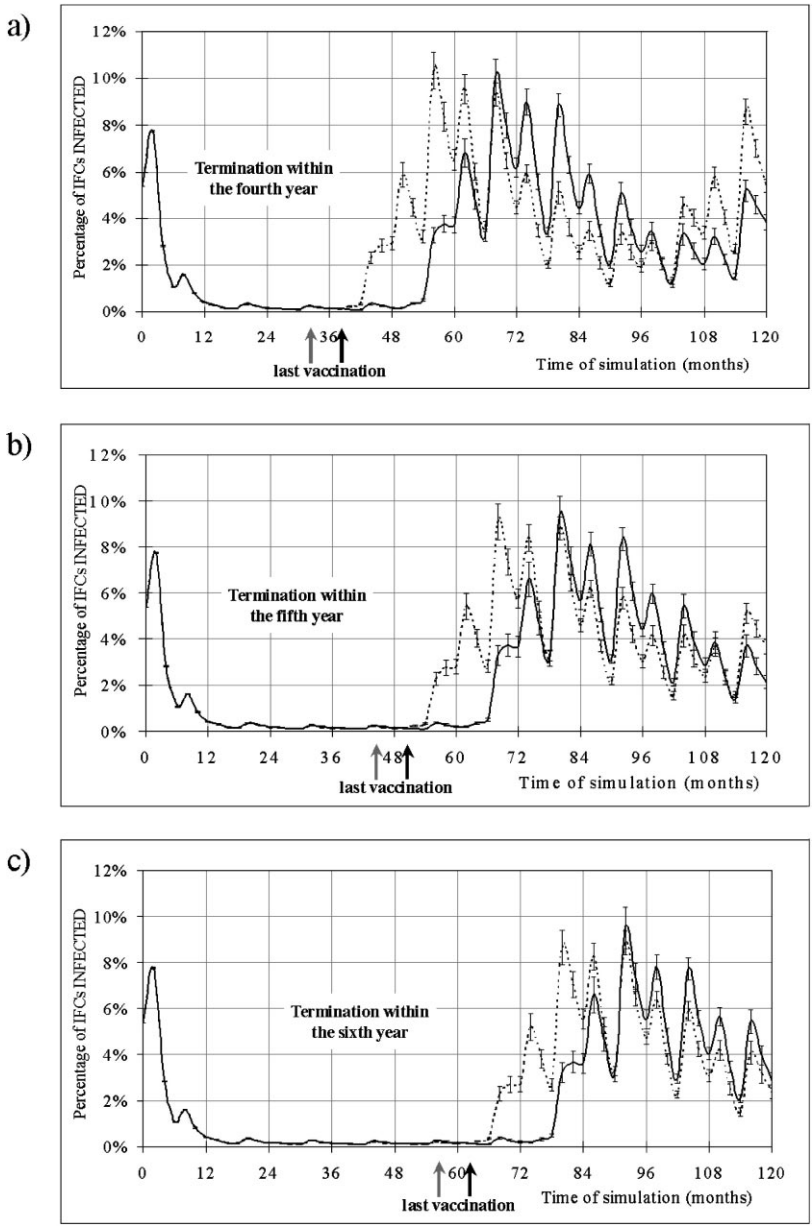

Fig. 3. The six temporal scenarios for termination of vaccination. The general base-line dynamics throughout the investigated parameter-space are depicted for one arbitrary parameter configuration ($P_{SI\langle neigh\rangle} = 0.34$; $P_{SI\langle mat\rangle} = 0.4$; $P_{SI\langle disp\rangle} = 1.0$; $P_{IE} = 0.8$; IR = 70%). Each diagram unifies termination in spring (solid line) and autumn (grey line): (a) in the fourth year of vaccination, i.e. after 6 (solid line) and 7 (grey line) campaigns performed; (b) in the fifth year, i.e. after 8 (solid) and 9 (grey line) campaigns; (c) in the sixth year, i.e. after 10 (solid) and 11 (grey line) campaigns. Graphs show mean values from 100 repetitions and the respective standard error bars.

Q1-A: Terminating vaccination within the fourth, fifth or sixth years triggers very similar dynamics of a post-vaccination outbreak. The resulting three pairs of time series show equivalent amplitudes growth except for a shift in time by 12 months (compare Fig. 3a and b) or 24 months, respectively (Fig. 3c).

Q1-B: If vaccination is terminated in spring (Fig. 3a, month 38) the number of infected IFCs increases just six months later (Fig. 3a, month 44). In contrast, if vaccination is terminated in autumn (Fig. 3a, month 44), the increase in infected IFCs emerges 12 months later (Fig. 3a, month 56). In addition, the first two peaks show a slightly higher amplitude in all cases of autumn termination (Fig. 3).

If rabies has persisted in the control area, the termination of vaccination triggers a new outbreak. The increasing level of disease prevalence in the field is eventually detected by surveillance and the second question asked, ''how long after termination would this happen?''

Q2: To figure out the potential trend of a post-vaccination outbreak, we determined from our simulations the time-series of the maximum and the minimum proportion of infected IFCs obtained over all parameter configurations (i.e. which caused low-level persistence in former simulations; see Section 3.1). These limiting lines form six spectra of possible post-vaccination outbreak dynamics, one for each termination scenario (Table 2; i.e. either after 3, 4 or 5 years of vaccination in spring or autumn, respectively). The spectra of possible dynamics cover the differences between the parameter configurations for a particular termination scenario. For visualization, Fig. 4 depicts one of the six possibility spectra: the autumn termination in the fifth year, i.e. with the last vaccination scheduled in spring (Table 2).

If vaccination were terminated in autumn (month 56), Fig. 4 shows that even with slow growth dynamic (i.e. lower limiting line), it takes only 24 months (i.e. 30 months after the last vaccination; month 80 in Fig. 4) before the outbreak displays the first noticeable peak likely to be detected by field surveillance (i.e. the proportion of infected IFCs exceeds 2% of all IFCs). After this time, the simulated epidemic shows regular temporal patterns, i.e. the bimodal annual cycle (Ulbrich, 1967; Toma and Andral, 1977; Curk, 1991), and the long-term cycle (Kauker and Zettl, 1960; Kaplan, 1985; Sayers et al., 1985). The five termination scenarios not depicted (see Table 2; available on request) show quite similar temporal characteristics. However, if vaccination were terminated in spring, the necessary period until detection could even be shortened to 18 months due to the occurrence of the first noticeable peak 6 months earlier compared to the autumn scenario (see above Q1-B and Fig. 3).

4.2. Spatial aspects

The last question addresses the area which needs to be vaccinated by emergency treatment and entails estimating the distance over which rabies is likely to spread from a small focus of infection by a sequence of dispersing fox generations. Fig. 5 shows the proportion of individuals (after up to four successive dispersal events) that exceed a given distance from the original point of departure.

Q3: The simulation experiment predicts that even after four consecutive dispersing generations (corresponding to 4 years), only a few of the simulated sequences of

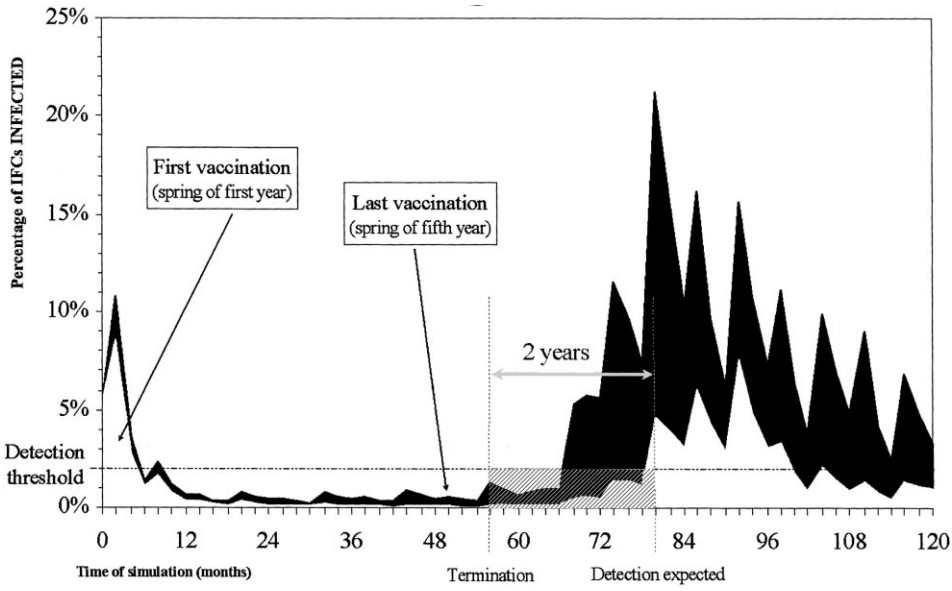

Fig. 4. The possible temporal course of a post-vaccination outbreak caused by low-level persistence of rabies if termination was scheduled in autumn of the fifth year of repeated vaccination. The dark possibility band reassembles different epidemiological circumstances covered in terms of different configurations for the model parameters in the simulations. The hatched area indicates the time-horizon of uncertain outcome from the terminated vaccination program.

movements (i.e. 1.5% after two, 3% after three or 6% after four dispersal phases) exceed in total the maximum distance covered by one dispersing generation (Fig. 5, at abscissa value 1, i.e. maxdist). Particularly, the end-points of all simulated two- (three- or four-) step dispersal sequences occurred within a distance of 136% (174 and 186%) of the maximum distance (Fig. 5, cross point of the respective graph with the abscissa).

Based on this result, we estimated the area required for emergency treatment stepwise according to the year after control termination within which a new rabid fox will be detected. Let us define 'maxdist' as the maximum dispersal distance ascertained for foxes in a specific region (i.e. 31 km from Goretzki et al., 1997). If a rabid fox is detected within the first year after termination, the source of infection (i.e. the parental den) is likely to be at most maxdist apart. At the same time, a second fox could have carried the infection in the opposite direction, again by a distance of maxdist. Then, the disease must be anticipated to be twice maxdist away from the detected rabid fox (Fig. 6). Because we cannot determine in which direction (i.e. angle) the original focus of infection was situated, our best suggestion is a hazard area covering a circle with a radius of twice (maxdist) around the detected rabid fox (see Bacon, 1981). The repeated use of this simple rule (i.e. radius = twice ($2 \times$ maxdist) within the second year or radius = twice ($3 \times$ maxdist) within the third year) provides a rapidly increasing hazard area causing the costs required for the vaccination of the determined area to increase dramatically.

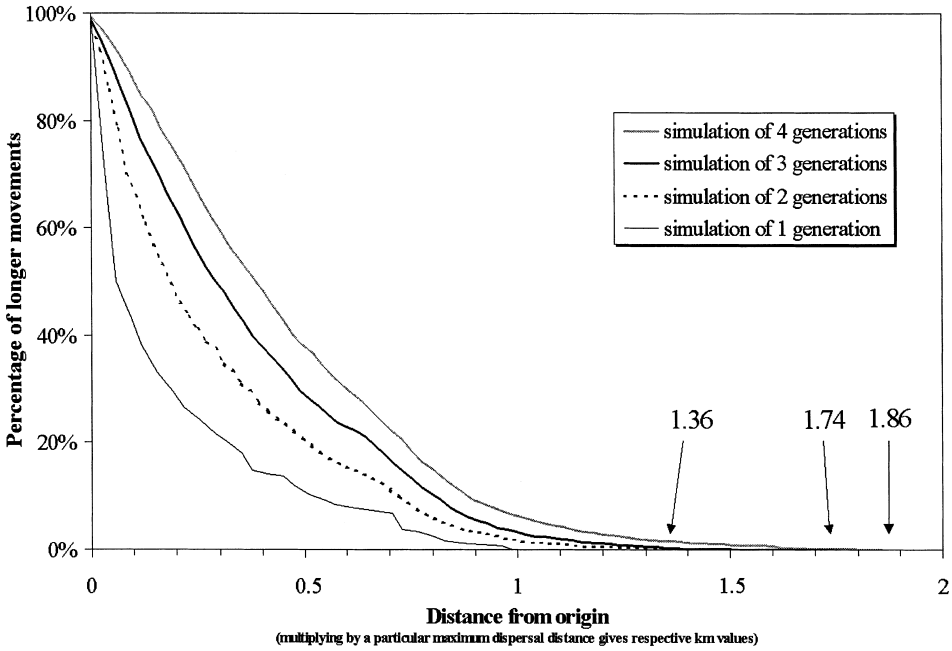

Fig. 5. Total distances covered by 2000 simulated dispersal movements of four consecutive generations (i.e. years). The graphs represent the probability to find longer total distances then a given distance from the origin (abscissa) after one, two, three or four generations (i.e. years) (the *x*-axis is scaled relative to the maximum distance found for the area of interest).

At this point, we make use of our simulation results: Hence, if the rabid fox is detected within the second year after termination, we insert twice (1.36 × maxdist) for the value for the radius of the circle instead of twice (2 × maxdist). This could be done because we found the maximum distance for two simulated successive dispersal events to be only 136% of maxdist and not doubled (Fig. 5). Particularly, the circle around a rabies case

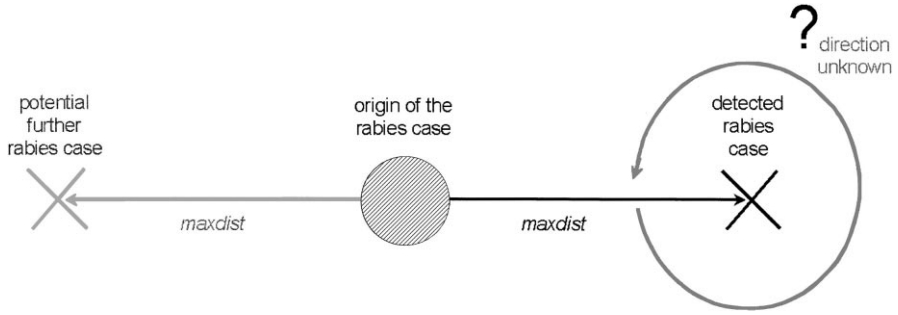

Fig. 6. Diagrammatic estimation of the maximum distance linking a detected rabies case to potential further infected animals. Because of uncertain direction for the graph (i.e. planar angle) the whole circle around the detected case might contain other infected animals.

detected within the second year after termination encompasses an area 54% smaller if the refined value for the radius is used (i.e. twice (1.36 × maxdist)) instead of the basic value (i.e. twice (2 × maxdist); the particular savings (2^2–1.36^2) of 2^2 gives 54% reduction). Respectively, within the third and fourth year the result (174 and 186%) provides circular hazard areas 66% ((3^2–1.74^2) of 3^2) and 78% ((4^2–1.86^2) of 4^2) smaller than if the basic rule would be applied. Finally, starting from the area within the first year (i.e. radius of twice (maxdist)) the trade-off left is either to keep the hazard area constant accepting 1.5, 3 or 6% of cubs leaving the emergency area potential infected or successively increasing the hazard area by 85% (i.e. (1.36^2–1^2) of 1^2), 64% and 14% to correct for the longer movements within the second, third and fourth years after terminating the vaccination program.

5. Discussion

At the end of the millennium, rabies control in western Europe has reached the point where the cessation of long-term and large-scale oral vaccination programs for foxes is being proposed due to the almost complete lack of rabies cases reported from controlled areas (Stöhr and Meslin, 1996; Schlüter et al., 1997; Müller, 1998). However, if rabies prevalence within a vaccination area was very low (i.e. $< 2\%$), field surveillance measurements might simply have failed to detect the disease due to sampling uncertainty (Braunschweig, 1980; Bacon, 1981; Schlüter and Müller, 1995) and erroneously indicate that control can be terminated.

Thinking further, due to the decreasing net benefit with increasing time of repeated vaccination (Selhorst and Schlüter, 1997), eventually every control program will be terminated regardless of the risk of persisting rabies going undetected. The resulting basic uncertainty concerning the final success of a control program will remain after termination either until an actual case is detected or for the purposes of this study until we can provide a temporal threshold criterion. Therefore, we tackled the initial question concerning this final decision:

5.1. How long after the last vaccination is a new rabies outbreak likely to be detected by usual surveillance?

Remember that European surveillance programs are designed to detect a 2% level of rabies prevalence in the investigation area with 95% confidence (Barrat and Aubert, 1993; Müller et al., 1994; Schlüter and Müller, 1995; Masson et al., 1996). Every rabies outbreak will exceed this threshold prevalence level and therefore eventually it will be detected (Davis and Wood, 1959; Wandeler et al., 1974; Steck and Wandeler, 1980). The results from our simulation now provide an estimation for the time horizon within which the post-vaccination outbreak must be detected if there was any. The first peak in the proportion of IFCs infected which exceeds the critical threshold occurs within two years after control termination for all of the time series (i.e. parameter configurations) investigated, even if the amplitude varies. Thus, within a time horizon of two years after termination, the post-vaccination outbreak would be detected. But, turning this around,

our results suggest that after two years without any rabies detection no post-vaccination outbreak could be associated with the termination. Consequently, two years of prolonged surveillance provides a final proof that the control program has successfully eradicated the disease (assuming for brevity that infected foxes cannot immigrate into the surveillance area). This kind of 'negative' proof gives the solution for the initial question and enables a serious termination of control programs. Finally, we can conclude that the risk of the post-vaccination rabies outbreak resulting from an overlooked low-level persistence of the disease — the worst-case-scenario (Thulke et al., 1997a) — reaches zero within the finite time interval of two years.

Within limited sub-areas (i.e. in the sub-area around the original focus), the actual prevalence of rabies could exceed the threshold level much earlier and seemingly provide a better decision measure. But, due to spatial sampling heterogeneity, if no rabid fox were detected we once again would not know for certain whether surveillance randomly failed the sub-area or no post-vaccination outbreak occurred. Hence, we refer to the slower but less-complicated indicator of overall prevalence within a total control area when analysing the simulation results in terms of the proportion of IFCs infected.

The simulations are based on the estimated decrease of immunization coverage. In particular, the decreasing proportion of immune animals follows the life expectancy of foxes in a hunted population (Stubbe, 1980) because we assume no decay in vaccine induced immunity over a temporal interval of one year. In our estimation, we assumed hunting to affect all age classes proportionally to size. The possible disproportionate killing of juvenile foxes by hunters was neglected due to the lack of data. In this situation, the immunization coverage in the fox population could decrease more slowly because older animals are still immune and alive. The estimated time span until the detectable recovery of a post-vaccination outbreak is then obviously prolonged at most to the maximum longevity of red foxes. But, there is much less evidence of the long-term selective killing of cubs in the literature (Stubbe, 1980; Goretzki and Paustian, 1982; Goretzki et al., 1997).

We have found a solution for the lasting uncertainty about the epidemiological situation in a control area at least as long as no new rabies case was detected after termination: after 2 years the program is completed. Therefore, we now exclusively concern ourselves with the situation that the vaccination is terminated although there was an actual but undetected low-level persistence of the disease. Indeed, we have small clusters of infection which trigger a post-vaccination outbreak when the immunisation shield decreases. The efficacy of rabies control after an outbreak is dramatically affected by the time until first detection (Bacon, 1981; Smith and Harris, 1991). To minimize the time until detection, we have asked:

5.2. When is the best time to stop a long-term, large-scale vaccination program?

The best time to stop a long-term, large-scale vaccination program would certainly be after the eradication of rabies, which is the aim of European rabies control. Unfortunately, complete eradication cannot be proven directly by field data (see Section 5.1. and Thulke et al., 1997a) and the required proof is possible only after an actual termination. Therefore, the question has to be modified into whether the point in time for termination

of vaccination can shorten the time until detection of an overlooked persistence of rabies in the control area. The problem has two aspects: the termination point within a given year of control (i.e. spring or autumn) and the number of years completed with biannual campaigns before termination is scheduled.

From the comparison of spring and autumn termination scenarios, we know that if vaccination is terminated in spring (i.e. with the final campaign in the previous year; see Table 2), 12 months were necessary until the first noticeable peak was observed compared to 18 months in the autumn scenario. To speed up the detection of the post-vaccination outbreak, we obviously will chose the spring termination. The reason for this striking difference relates to the regular seasonal pattern in fox biology (i.e. birth pulses always reduce the immunisation coverage in the spring and the annual dispersal provides long-distance transmission by moving cubs always in autumn; see Section 2.1). When we terminate by omitting the spring campaign, the non-immunized offspring generation of the very same year might propagate the disease from the few local clusters of infected fox groups during autumn dispersal resulting in a noticeable disease upturn 6 months after termination or 12 months after the last campaign. In contrast, if vaccination is terminated in autumn, the next non-immunized generation only occurs in the following year and the relevant long-distance dispersal of infected cubs takes place 18 months after the last campaign. Consequently, the termination of control in spring actually shortens the time horizon until likely detection of a post-vaccination outbreak of the disease.

For the proportion of IFCs infected, we predict higher first peaks under the autumn termination scenarios compared to the spring termination (see Fig. 3a–c). Indeed, in the autumn termination scenario, the disease transmission by neighboring IFCs during the following 12 months slightly increases the number of infected IFCs surrounding the initial focus due to the reduced immunization coverage after birth event. This relatively small increase is then multiplied by the dispersing cubs which results in the higher first peaks (see Fig. 3a–c). It is striking to us that the combination of the spatial-clustering characteristics of the low-level persistence of rabies (Tischendorf et al., 1998) and the different spatial scales on which annual fox activities act (Jeltsch et al., 1997) can provide reasons for the differences observed between the two simulated temporal termination scenarios in spring and autumn.

The similar temporal dynamics of the simulated outbreaks through all years of termination (i.e. within the fourth, fifth or sixth years of biannual campaigns) provides no improvement for the time until detection of a post-vaccination outbreak. On the other hand, in view of the speculated net benefit, this result seems to argue for the earliest termination of an control program (i.e. if no further case was detected) because prolongation of vaccination does not alter the dynamics of a post-vaccination outbreak but certainly will increase the costs. However, the post-termination outbreak from a low-level persistence of rabies is only one possible scenario within a post-vaccination area (Tischendorf et al., 1998). If no infected foxes immigrate and no low-level persistence of the disease has been ascertained, the chance of eradication should not be overlooked (which rises with prolonged time of repeated vaccination campaigns; see Tischendorf et al., 1998 for details). In fact, the chance to eradicate the rabies epidemic reaches its maximum until the sixth year of a long-term and large-scale vaccination program

(Tischendorf et al., 1998) and, as our results indicate, within this time-horizon the consequences of wrong termination (i.e. due to an overlooked low-level persistence of the disease) do not alter between years. Hence, the year of actual termination could exclusively be geared to increase the chance of eradication gained per year of prolonged vaccination.

To sum up, the actual number of years under control before termination does not alter the characteristic dynamic of a potential post-vaccination outbreak. However, termination of a vaccination program after final baiting in autumn (i.e. spring termination scenario) hastens a new outbreak by six months, reduces the time span between termination and detection of the outbreak and is, therefore, encouraged by the results.

5.3. What size area needs to be vaccinated by an emergency treatment and how does it depend on the time since the last regular vaccination?

The possibility of rabies cases going undetected after an intensive vaccination program raises the immediate question of how to deal with a post-vaccination outbreak. A newly detected rabies case within a post-vaccination area indicates other infected animals. To provide emergency treatment, the area likely to contain all possible infected foxes could be intensively re-vaccinated. We discuss the sufficient area for emergency vaccination on the basis of the time since termination of vaccination.

The intuitive answer to the question gives an circular area that always will include any infected fox related to a disease focus within the control area. Particularly, if one determines the maximum distance that cubs will disperse in a region under control for rabies, the circle with radius of twice this maximum distance around the detection covers for sure the origin of the detected fox and all its siblings from the very same year that potentially also carry the disease. However, we require an equivalent estimation for the second year after termination. Indeed, as discussed above, a potential post-vaccination outbreak could be identified until two years after the termination (independent of whether there was a spring or autumn termination). The extension of the basic rule, however, will result in an impractical large area not related to the idea of emergency measurements. Therefore, we apply our simulation results to reduce the circular hazard area around the detected case by 54%. For example from field data (Goretzki et al., 1997; i.e. with 31 km as maximum dispersal distance), the refined area for emergency vaccination would cover 22,336 sq km instead of the 48,305 sq km resulting from the doubled basic rule. Compared to a total area of 108,000 sq km vaccinated for six years in the eastern part of Germany (Stöhr and Meslin, 1996), the area which has to be baited in the worst case of a post-vaccination outbreak is dramatically reduced.

Applying vaccination to the suggested circular hazard area could restrict the spread of a new outbreak and reduce the risk for the surrounding area as well as the costs of emergency vaccination. However, the actually necessary hazard area is likely to be smaller than the suggested circle. Our results are based on the distance distribution found by Goretzki et al. (1997) for a particular region in Eastern Germany. The data are based on annual distance records for marked ($n = 1118$) and recaptured ($n = 213$) foxes between 1988 and 1993. Obviously, the distances measured by this approach do not reflect only the cubs' dispersal in autumn for the respective individuals. Consequently,

when simulating the autumn dispersal of four consecutive generations in our study (i.e. drawing four times from the distance distribution), some of the model individuals will disperse too far which increases the resulting distance and eventually gives an overestimated radius suggested for the hazard area. Additionally, we apply ''twice the simulated maximum distance'' as radius for the hazard area assuming the possibility that the maximum distance is covered in the opposite direction (relative to the detected case) by any of its relatives which seems to be a possible but unlikely event. Both assumptions lead to a potential overestimation which makes the result more conservative. But, we approximate the time-dependent distance spread of rabies by the respective number of generations dispersing in autumn. This approach mimics a direct transmission of the disease between consecutive dispersers which is naturally impossible due to the short disease cycle of rabies (incubation + infectious period <2 months; Bacon, 1985; Charlton, 1988; Aubert, 1992). Therefore, in the field, neighborhood infections will maintain the disease between two consecutive dispersal periods. In a post-vaccination area, these events are rare and contribute a negligible amount to the total spreading distance compared to the cubs dispersal (David and Andral, 1982; Garnerin et al., 1986). Nevertheless, choosing the more-conservative estimation for the necessary radius, we cover the uncertainty about disease spread throughout the year and provide a safe-side suggestion for the area of hazard management.

Two improvements concerning the emergency vaccination strategy are subject to further research. Firstly, spatial landscape heterogeneity (i.e. dispersal barriers) certainly influences the spread of rabies from a focus of infection (Ball, 1985; Moore, 1999). The projection of our model on real landscape data using Geographic Information Systems might lead to very particular hazard areas in real landscapes. Secondly, the actual execution of an emergency vaccination campaign, i.e. the number and schedule of campaigns during the year or bait density, needs to be analyzed regarding its efficacy in eradicating a local outbreak.

To our knowledge, this study is the first explicit attempt to consider the consequences of the transition from a highly vaccinated to a non-vaccinated fox population (Pech and Hone, 1992; Barlow, 1995). The simulation results outlined in this paper provide an initial basis which could serve as a guide for emergency vaccination programs. Our simulation study focuses on the worst-case scenario of an undetected low-level persistence of rabies within large coherent vaccination areas. Immigrating infected foxes are most relevant near non-vaccinated areas, indicating the need for some form of prolonged borderline control (Murray and Seward, 1992; Aubert, 1992; Brandl et al., 1994). However, the results presented can easily be extended to foxes potentially immigrating into an area where the immunization level is declining due to a terminated control program.

6. Conclusions

This study provides an improved understanding of the spatio-temporal dynamics of a rabies outbreak after a long-term, large-scale control program with biannual scheduled vaccination campaigns has been terminated resulting from potentially overlooked low-

level persistence of the disease or the immigration of infected foxes. The results of the simulation study support the following conclusions:

1. The dynamics of a post-vaccination outbreak are not influenced by the year of vaccination termination (i.e. after 3, 4 or 5 years) but the time-span between termination and outbreak is 6 months shorter if the vaccination program is terminated with autumn campaign rather then spring campaign. On the basis of the simulation results, we therefore recommend termination after an autumn campaign because an earlier chance of detecting a new outbreak ultimately diminishing the hazard area it is necessary to threat. The year of termination itself should be aimed towards improving the chance of eradication.
2. Due to the consistent dynamics of all post-vaccination outbreaks investigated, a final decision concerning the success or failure of the vaccination program can be made two years after the last vaccination campaign. By this time, rabies will either have resurged and been detected or will have been eradicated. However, this conclusion neglects the complicating possibility of infected foxes immigrating from surrounding areas.
3. If a rabid fox is detected within the first year after terminating vaccination, the hazard area around the point of detection should encompass at most a circle with a radius of twice the maximum dispersal distance found for that region. If detection occurs in the second year, the area of emergency treatment must be enlarged by 85%. The rule for determining a hazard area applies both in the case of undetected low-level persistence and when infected foxes immigrate from unvaccinated areas into a rabies-free post-vaccination area.

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