CONTROLLING RABIES IN FOXES BY ORAL VACCINATION – LEARNING FROM A SIMULATION MODEL

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Rabies is one of the oldest diseases described in the world. In recent years European countries have made huge efforts to combat this zoonosis (Stöhr & Meslin, 1996**;** Meslin, 1997). Rabies control measures traditionally focused on population reduction designed to break the infection chain (e.g. gassing, poisoning, trapping and shooting). However, most of the control measures proposed failed to permanently reduce the host population below the critical threshold at which rabies ceases (e.g. Winkler & Bögel, 1992). The development of effective anti-rabies vaccines heralded a new control measure. Initial field studies in the 1970s in Switzerland (Steck et al., 1978) demonstrated the oral vaccination of the fox population to be the measure of choice for successful rabies control. Consequently, over the past two decades, research into the control of sylvatic rabies has chiefly concentrated on developing methods and strategies for the oral vaccination of wildlife rabies vectors (Masson et al., 1996**;** Schlüter et al., 1997).

Various modelling studies have been conducted to support rabies control and contingency planning (Smith & Harris, 1991**;** Pech & Hone, 1992). Progressing with the evolution of applied mathematics and computer power, rabies models have changed from mimicking cycles of fox biology (Smart & Giles, 1973) via abstract analytical models (Anderson et al., 1981; Murray et al., 1986) to detailed, complex individual-based models (Voigt et al., 1985**;** Smith & Harris, 1991). Yet although each model is appropriate for analysing specific questions, none are suitable for tackling all rabies-related problems at the same time Nevertheless, recent questions have arisen at the end of the millennium concerning the systematic eradication of rabies in Western Europe by exhaustive vaccination programmes. To tackle these questions, modelling methods are required which could assist decision-making in future rabies control policy.

We have developed a disease-related, spatially explicit rabies model. It is based on modern modelling techniques and enables comparisons with the findings gained from the literature on rabies modelling (Thulke et al., 1999a). In this paper we will discuss three aspects of rabies epidemiology in particular which are elucidated by our simulation studies. Firstly, although random walks of rabid foxes are thought to play a major role in spatial rabies spread, simulations by Jeltsch et al. (1997) allow a revival of this discussion and point to a different conclusion. The next two items particularly relate to the anti-rabies vaccination of red foxes. Secondly, the effect of heterogeneity in the coverage

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of vaccine bait is often discussed in the context of rabies control. Therefore we applied our model to scenarios with spatially heterogeneous population immunity. Comparison with results by Tischendorf et al. (1998) for the homogeneously vaccinated rabies-fox-system provides further understanding. Thirdly, we extend our investigations concerning the potential persistence of rabies at low, hardly detectable prevalence levels despite the long-term and large-scale vaccination of foxes (Tischendorf et al., 1998). Having discovered this potential source of failure, we tackle the need for ongoing control strategies to eliminate uncertainty about the final proof.

MODEL AND METHODS

The model

We depict the host population spatially throughout 'infection communities'. The concept of an Infection Community (IFC) reflects the establishment of small temporary social fox communities (Storm & Montgomery, 1975**;** Niewold, 1980) in which contact rates can be assumed high enough (White et al., 1995) to spread a potential infection of one group member throughout the whole group. This eliminates the need to deal with less well-known biological and epidemiological factors, such as the territorial behaviour of red foxes, contact rates, basic reproduction rates or individual differences in incubation period (Anderson et al., 1981**;** Voigt et al., 1985**;** Murray et al., 1986**;** Smith & Harris, 1991). Moreover, because the definition of IFC is not area-dependent, our model output is resilient to varying population densities.

We use a two-dimensional, grid-based model to arrange the IFCs in space. Each cell represents one IFC. Each IFC can have precisely one of the following states (Fig. 1): **S**usceptible (IFCs in which all members are susceptible to an infection), **I**nfected (IFCs in which at least one animal is infected) and **E**mpty (extinct IFCs as a result of disease mortality). The grid of IFCs was exposed to vaccination. To accomplish this, we introduced three new states representing the straight proportional immunisation of IFCs (states **EM**, **SM** and **IM** in Fig. 1). The actual proportion within 'partially immunised' IFCs is defined by the mean immunisation level (IR).

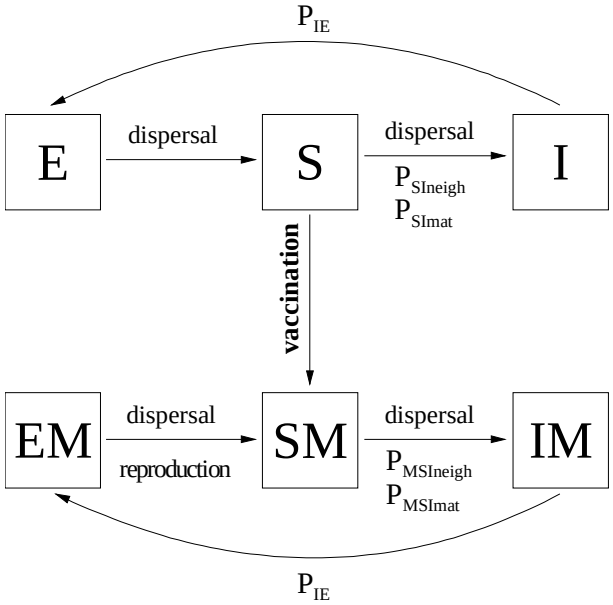

Fig. 1 The six possible states of IFCs. E=empty; S=susceptible; I=infected; M=iMmune after vaccination, i.e. IFCs in state SM are partially immunised according to assumed immunisation (IR). The arrows indicate the possible state transitions. P_{SI}=probability of infection; P_{IE}=probability of disease related extinction within one time-step (after Tischendorf et al., 1998).

Rabies spread is modelled by three mechanisms: 'neighbourhood infection', 'mating' and 'dispersal'. By 'neighbourhood infection' a susceptible IFC is infected by adjacent IFCs with a probability of P_{SI} representing the most local spread of rabies via infection caused by interactions and conflicts between animals of neighbouring IFCs. By 'mating' we refer to the increased spatial activity of itinerant adult males during the rut (Toma & Andral, 1977). Therefore, during 'mating' an infection could symbolically be carried over from up to three IFCs away when evaluating the infection event for a susceptible IFC. The annual dispersal of fox cubs is modelled in an individual-based manner in the time-step of 'dispersal'. The number of dispersing cubs (Allen, 1984) and the distribution of dispersal distances are based on field data (Trewhella et al., 1988**;** Goretzki et al., 1997). Because immunisation reduces the susceptible part of the host population, i.e. the number of potentially infective contacts, the onset of 'vaccination' linearly reduces the infection probabilities applied for the spreading mechanisms (Tischendorf et al., 1998).

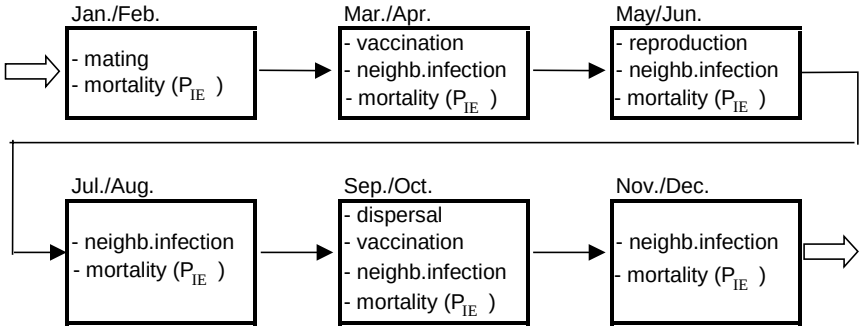

Fig. 2 The schedule of individual processes within the six model time-steps representing one year. Reproduction occurs in the third step because of the delay between birth and effective susceptibility, i.e. when an infection actually can be introduced in the IFC via the offspring.

We use a temporal scale of two months, which is suitable for the annual rhythm of red foxes and the dynamics of rabies infection (Fig. 2).

Simulation experiments

The role of rabid foxes: Jeltsch et al. (1997) identified the specific interaction of short-distance rabies spread (e.g. neighbourhood infections) and rare long-distance spread (e.g. annual dispersal) to be responsible for the formation of the observed spatial wavy pattern of rabies epidemics (Steck & Wandeler, 1980**;** Macdonald, 1980). Here we use projections of the pattern simulated on a grid of 600x300 cells over up to 600 time-steps, either with the described model or with suppressed 'dispersal' but explicit modelling of random walking rabid foxes in each time-step. We compare the simulated pattern with results from the literature (Källen et al., 1985; Murray et al., 1986).

Heterogeneous immunisation: We compare the probabilities of eradication for simulations based on a homogeneous and spatially heterogeneous immunised population. The differences allow the effect of heterogeneity in the immunisation level to be quantified. The reference data are taken from Tischendorf et al. (1998). Both simulation experiments are conducted on a square lattice of 140x140 cell over 120 time-steps with 'vaccination' (i.e. 10 years of repeated vaccination campaigns). All model parameters were varied over their meaningful range (see Tischendorf et al., 1998) reflecting a whole set of different epidemiological set-ups (cf. Spear & Hornberger, 1983**;** Fahrig, 1991). For each set-up of parameter values, 100 simulation runs were performed and from the 100 repetitions the frequency of complete eradication was assigned to the parameter configuration. Finally, a measure of success is defined as a function of the mean immunisation level [i.e. IR = 60%-80%; step 2%] in the vaccination area: For each level of immunisation (i.e. value of IR), the relative frequency of

eradication (RFE) was calculated from the respective subset of parameter configurations by averaging their frequencies of eradication (Fig. 3).

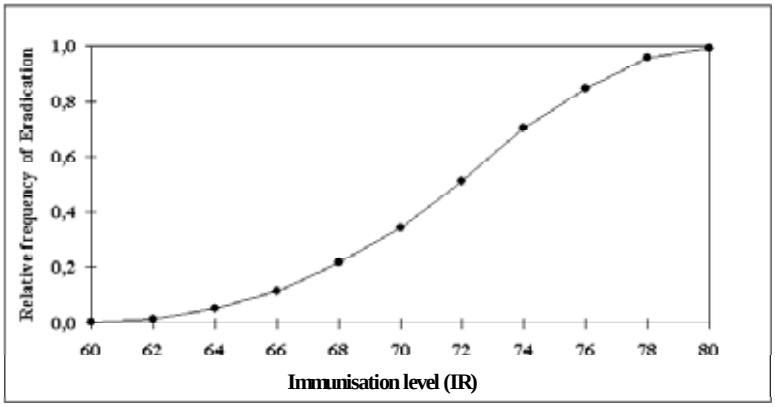

Fig. 3 The relative frequency of eradication (RFE calculated as explained in the text) for the investigated values of mean immunisation level in the homogeneous scenario (after Tischendorf et al., 1998).

The spatial homogeneity in immunisation is achieved by assuming the given value IR to hold for any single IFC, i.e. 70% of the animals in any susceptible IFCs are immune. Now heterogeneity is introduced by an algorithmic selection (Plotnick & Gardner, 1993) of a proportion of all IFCs (parameter no_bait) that are excluded from immunisation. Obviously, no_bait equals 0% in the homogeneous scenario and the value of the parameter determines the total *amount of perturbation* in bait coverage. The selecting algorithm (Plotnick & Gardner, 1993) is governed by a second parameter (frag) which determines the *fragmentation of perturbation* (cf. Fig. 6), i.e. whether it is rather clumped (Fig. 6a) or evenly distributed (Fig. 6c). At the beginning of each simulation run a random pattern of IFCs is excluded from immunisation (Fig. 6a-c). As a consequence of exclusion, the effective immunisation level (IR_eff) for any non selected IFC must be adjusted depending on the assumed mean immunisation level IR, i.e. IR_eff = IR/(1-no_bait/100).

Large-scale and long-term oral vaccination of red foxes: Previous simulation experiments have revealed that the immunised fox-rabies system can eventually harbour the low-level persistence of the disease (Fig. 4) despite prolonged vaccination (Tischendorf et al., 1998). To examine the

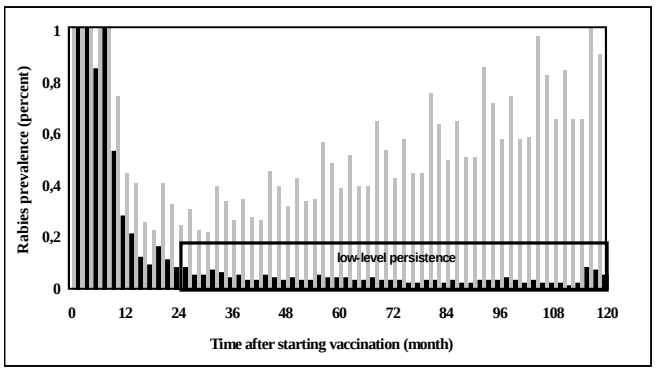

Fig. 4 Definition of low-level persistence by an time-series of rabies cases shown by way of example. After two initial years the overall prevalence in the simulation area neither exceeds 0.2% nor tends to zero despite continuous immunisation of 70%. By contrast, the shaded background shows an epidemic which clearly recovers despite vaccination (IR=64%; after Thulke et al., 1997)

characteristics of the ignored persistence of rabies after termination of vaccination, we conducted another simulation experiment (Thulke et al., 1999b). With all parameter configurations that in our previous simulations (Tischendorf et al., 1998) had produced a low-level persistence of rabies, 100 new runs were performed on a 140x140 cell lattice and vaccination was terminated after 30 time-steps (five years). The development of the new outbreak was reported by the time-series of infected IFC. The necessary model adjustment focuses on the immediately reduction of the immunisation level due to the turnover of the fox population. To deal with this, a six-valued step function was derived from the life statistics for red foxes (Stubbe, 1980) to describe the consecutive reduction in IR, i.e. the remaining percentage of immune animals in the population (for technique see Selhorst, 1996**;** Thulke et al., 1999b).

RESULTS

The role of rabid foxes: The results on which our discussion is based are presented graphically (Fig. 5) by the number of infected IFCs recorded at different locations. In the case of individually modelled dispersing animals (Fig. 5a), distinguished spatial waves follow after the front wave. Whereas in cases without explicit dispersing animals (Fig. 5b) no regular wavy spatial structure emerges behind the front of the epidemic. The latter mimics the simulation of rabies spread by a diffusion approach (Källen et al., 1985; Murray et al., 1986; Yachi et al., 1989), i.e. by performing each time-step with both neighbourhood infection and the random walking of rabid foxes the disease diffuses from infected areas into non infected adjacencies with no variability over the year.

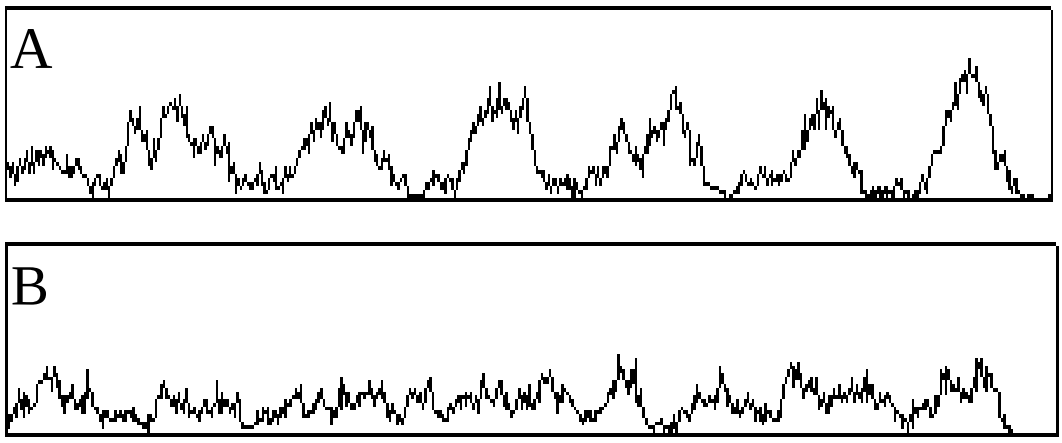

Fig. 5 The one-dimensional projection of a rabies epidemic perpendicular to the spreading direction simulated on a 600x300 cell lattice (after Jeltsch et al., 1997). A) The model includes the individual-based dispersal of foxes once a year. The movement of rabid foxes is aggregated in the probability of standard neighbourhood infection. Snapshot after 120 time steps (20 years). B) The movement of rabid foxes is modelled explicitly by performing individual random walks originating in infected IFCs. By contrast individual-based dispersal is excluded, i.e. the spread of the disease by dispersing cubs is restricted to the standard neighbourhood infection. This version of the model relates to the approach of Källen et al., (1985) and Murray et al., (1986) which neglects the importance of dispersing foxes and suggests only rabid foxes to be the driving force behind the spread of disease. Snapshot after 216 time-steps (36 years).

Heterogeneous immunisation: We quantified failure in immunisation by two measures: the total amount (no_baits) and the degree of fragmentation (frag) of perturbation. We found the relative frequency of eradication (RFE) to rise as the values of fragmentation increase (Fig. 6d). However, two different effects emerge. If the fragmentation value is small (i.e. perturbation appears in coherent clusters, Fig. 6a), the chance of disease eradication (RFE) decreases compared to the homogeneous scenario (Fig. 6d, left). On the other hand, larger fragmentation values (i.e. perturbation appears rather uniformly distributed, Fig. 6c) increases the RFE beyond the value found for the homogeneous reference (Fig. 6d, right). It is noteworthy that in the latter case disease eradication is favoured by perturbation. Both effects intensify when the assumed amount of perturbation (no_bait) increases (Fig. 6d, crossed vs. circled graph).

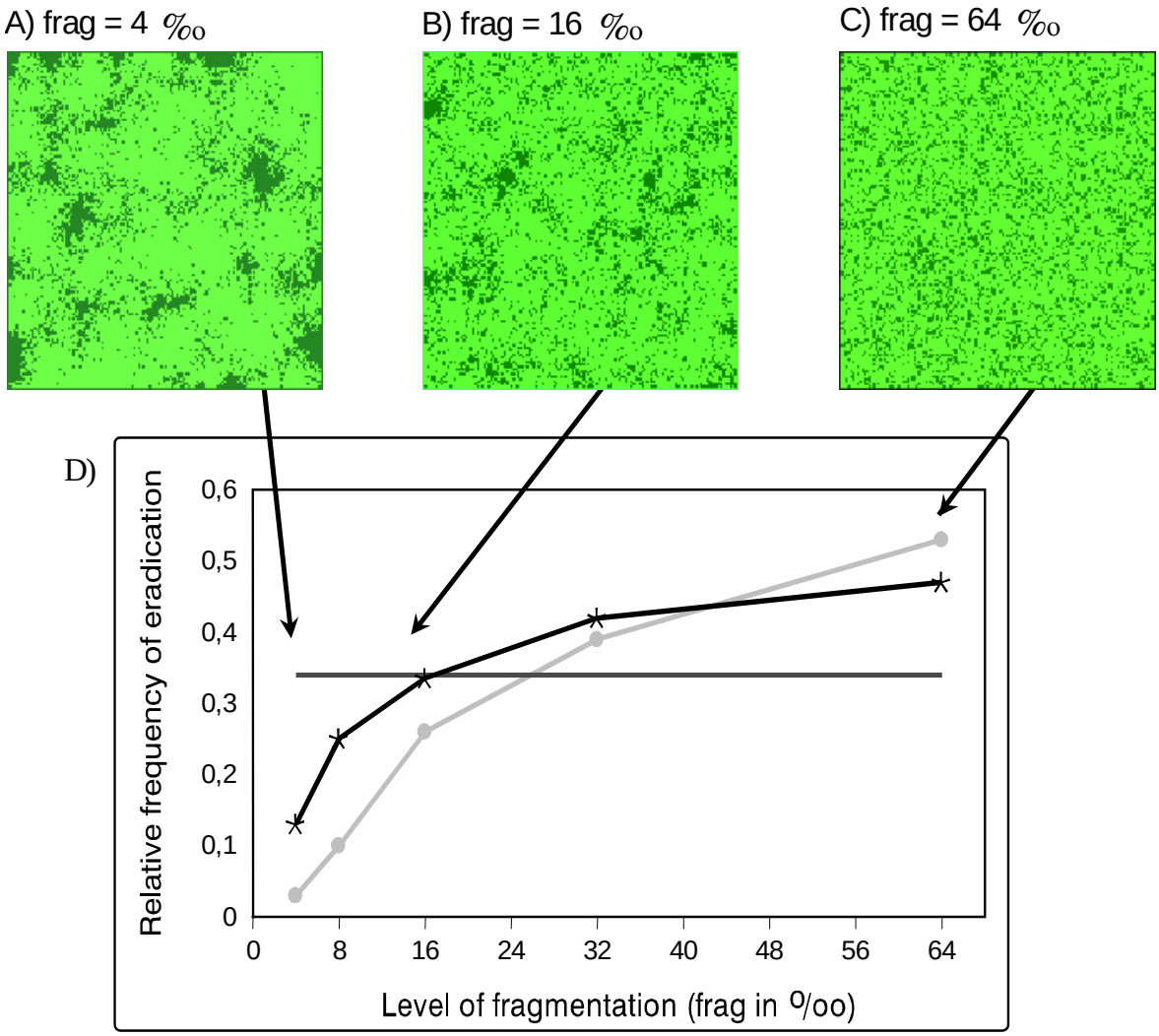

Fig. 6 Consequences of heterogeneous bait coverage for the eradication efficacy of the long-term and large-scale vaccination of foxes. A)-C) Random selection patterns depicted by way of example determining the set of IFCs which are excluded from immunisation in one simulation run. Although the fragmentation of perturbation (frag) increases from A) to C), the total amount remains constant (no_bait = 20%). D) Straight line: RFE value for the homogenous reference (from Fig.3). The other graphs show the RFE values for the increasing degree of fragmentation (frag) for one particular amount of perturbation (black line crossed: no_bait = 10%; grey line circled no_bait = 15%). Mean (overall) immunisation level (IR) remains constant for all simulations and equals 70%.

Large-scale and long-term oral vaccination of red foxes: The potential dynamics of low-level persisting rabies following the termination of a vaccination programme is summarised in a band of time (Fig. 7). This possibility spectrum is spanned by all the time-series resulting from our

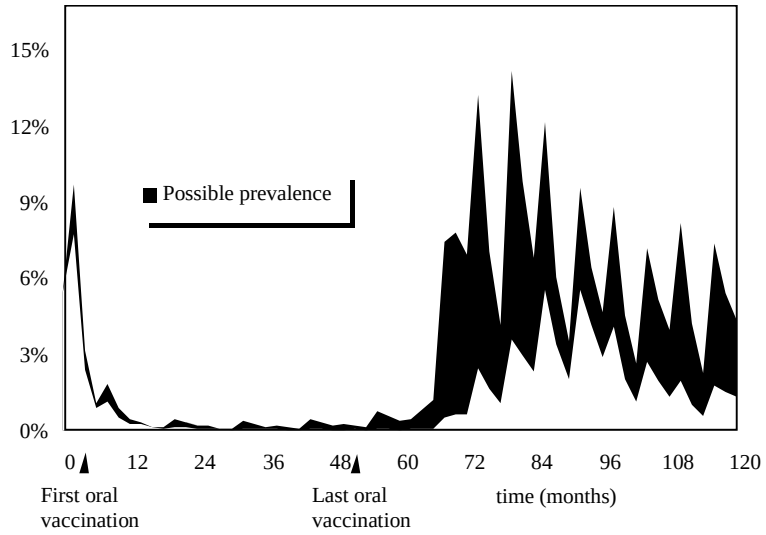

Fig. 7 Spectrum of simulated time-series for overall rabies prevalence in a 140x140 area. Immunisation started in year one on a standard spatial scenario and terminated within the fifth year, i.e. after month 50 (after Thulke et al., 1999b). All parameter configurations that previously proved to be linked to the low-level persistence of rabies were included, i.e. different epidemiological (actual immunisation level) and biological (mean litter sizes, contact rates) circumstances were taken into consideration.

simulations (Thulke et al., 1999b). We found, that during the time-steps of vaccination the bandwidth is small and after the offset of 'vaccination' the variability of the epidemic course increases. More generally, however, at least two years after the last vaccination the lower bound of rabies prevalence spectrum clearly passes the 2% value and tends into regular cyclic dynamics (Fig. 7). Therefore the new outbreak ought to be detectable as was the epidemic before control started.

DISCUSSION

Within this paper we unify particular aspects of rabies epidemiology. Based on rabies models evolving with respect to the scale of the questions addressed (Thulke et al., 1999a), we gained the results from our systematic simulation studies (Jeltsch et al., 1997**;** Tischendorf et al., 1998**;** Thulke et al., 1999b; Tischendorf et al., forthcoming).

The role of rabid foxes: The name of the disease stems from rabid foxes as they express abnormal behaviour (Charlton, 1988) and spontaneous aggressiveness (Macdonald & Voigt, 1985). Although it is well documented that only half of all infected foxes exhibit rabid symptoms (Bacon, 1981), rabid foxes are often cited as a major factor in the spread of the disease as they move around randomly during the clinical phase (e.g. Toma & Andral, 1977). Some authors exclusively refer to rabid foxes when they model rabies spread in space (Källen et al., 1985**;** Murray et al., 1986). The infection is diffused throughout the host population uniformly in time. By contrast, Jeltsch et al. (1997) found the coupling of two transmission processes from different spatial scales to be responsible for the formation of consecutive spatial waves, the typical pattern of rabies spread (Sayers et al., 1977; Hengeveld, 1989). Short-distance neighbourhood infections are the driving force behind disease transmission throughout the year. However, additional rare events (Jeltsch et al., 1997) of long-

distance transmission occur during dispersal, i.e. in autumn infected cubs move a long way compared to the tail of dispersal distance distributions (Trewhella et al., 1988**;** Goretzki et al., 1997). Without the temporal differences in the spatial scale of rabies spread, the disease pattern loses its wavy spatial structure just behind the front wave (Fig. 5b; cf. Källen et al., 1985**;** Murray et al., 1986). Källen et al. (1985) refer to varying incubation periods not considered in their model when reasoning the rapidly damped out front wave. Although Murray et al. (1986) added an incubating class to the model, they again found rapidly damped out rabies waves. Consistent with this, we found a damped out front wave with our model as long as we had only incorporated a diffusion-like disease spread by neighbourhood infection (Thulke et al., 1999a). Indeed, we only found the pattern of repeated advancing waves when potential spreading distances changed between the dispersal phase and the remaining year (Fig. 5a).

Rabies control planning needs very efficient (emergency) strategies in cases when a new outbreak occurs within a previously rabies-freed region. The interaction between the time spent until initial detection and possible spatial spread determines the hazard area after an outbreak (Bacon, 1981). Now, if we think about spatial rabies spread in a purely diffusion-like manner (Källen et al., 1985; Muray et al., 1986; Gardner et al., 1990), we would disregard any variability in time. Consequently, with respect to the time-dependence of potential spreading distance over the year, we would exclude useful information from management planning by the diffusion approach. Particularly in view of control planning, we explicitly refer to the importance of coupled short-distance and long-distance transmission events over the year, the basic feature of spatial rabies spread.

Heterogeneous immunisation: Our simulation studies concerning the chance of rabies eradication by the oral vaccination of foxes so far have been based on the assumption of spatial homogeneous control efficacy (Tischendorf et al., 1998). However, heterogeneity is a multifaceted issue of natural features and impedes not only processes in wildlife epidemiology. Enquirers anticipate that vaccination efforts closely depend on the potentially perturbed immunisation level in the fox population. Such disturbances are commonly thought to be related to technical errors, i.e. inaccurate aircraft navigation, wind-shifted bait, bait disruption or hand-baiting (Breitenmoser & Müller, 1997). Consequently, we tried to adjust our simulation results to the potential impact of heterogeneous immunisation.

In order to determine the influence of spatial heterogeneity, we may have used GIS-related approaches. However, any empirical map only represents a singularity of the infinite number of different possible combinations of factors that finally impede bait uptake. If general implications are necessary for further rabies control policy, such a restriction to one particular circumstance seems less helpful. Instead, we generate random spatial patterns of subareas where foxes are assumed to be excluded from immunisation and neglect the respective cause. Judging by the results presented we link a rabies-related quantitative description of heterogeneity (i.e. the amount of failed immunisation and its fragmentation in space) to control performance measure (i.e. the probability of eradication). We found that in general, heterogeneity is not necessarily disadvantageous for successful rabies eradication. However, we found two opposite effects of heterogeneous population immunity depending on whether the amount of failure appears clustered in a few coherent subregions (frag small) or is uniformly distributed over the whole area (frag large).

In detail, if bait coverage fails in coherent subregions (frag low, Fig. 6a) e.g. by vaccine failure due to logistics, then the chances of final disease eradication worsen compared to homogeneous reference (Fig. 6d). This is due to potential microepidemics within the subregions. The uncontrolled disease inside the subregion causes isolated cases in the partially immunised surroundings (cf. the situation on the border between Germany and the Czech Republic over the past few years). But in turn the neighbouring cases reintroduce the disease into the subregion if the population inside it has regrown. This mechanism could increasingly prevent rabies from eradication if subregions became larger (Fig. 6d).

Now we turn to higher degrees of fragmentation (Fig. 6c) e.g. by wind shift. The subregions with failed immunisation are no longer large enough for self-contained microepidemics. However, potential infected foxes within the well immunised part of the total area have a low chance of transmitting the infection unless they contact animals from a non-immunised group. And continued, the solitary (i.e. fragmentation is high) non-immunised fox group will soon be completely infected and die out within a short time-horizon. Therefore, it is unlikely that the disease will be retransmitted into the well immunised surroundings, but will instead cease with the solitary fox group. This phenomenon of 'catching rabies seeds from the immunised area' accounts for the increasing probability of disease eradication if the spatial distribution of baiting failure changes to uniformity. Finally, the probability of eradication exceeds the homogeneous reference value (Fig. 6d) because the positive effect of small uniformly distributed failure in immunisation is combined with the higher immunisation level within the baited area (IR_eff) relative to the homogeneous reference. Nevertheless, the mean level of immunisation (IR) used as a control quality measure in the field is equally determined for all simulation scenarios.

Large-scale and long-term oral vaccination of red foxes: We conducted a simulation study examining the spread of rabies within an immunised fox population (Tischendorf et al., 1998). We found that in the worst case rabies persists within the vaccination area even at an average immunisation level of 70% (Tischendorf et al., 1998). However, practicable surveillance measures would reflect low-level persistent rabies either as sporadic, solitary cases or as an apparently rabies-free area (Thulke et al., 1997). Consequently, field data cannot reliably demonstrate the conclusive success of a vaccination programme. Even if no rabid foxes have been detected, the final termination of control seems an impossible strategic decision owing to continuing uncertainty. Furthermore, if for economic reasons the apparently rabies-free state of a control area results in termination, emergency measurems must still be kept ready for worst-case management. But for how long must the logistics for emergency activities be maintained on standby?

Obviously, emergency measures need not be kept ready longer than the time it would take for a post-vaccination epidemic to recover at a definitely detectable level of prevalence. However, the detection of an uncontrolled rabies epidemic due to typical prevalence levels is guaranteed by practical experience. The time any post-vaccination epidemic needs to recover beyond the respective limits of certain detection is provided by our simulation result. The potential worst-case scenario would definitely be detected by newly recorded rabid foxes within two years after the last vaccination campaign (cf. Fig. 7). The simulation result therefore provides a basis for political management decisions in the context of areas suspected to be rabies-free after long-term, large-scale vaccination. We can thus assure both conclusive proof of whether an eradication programme has succeeded (assuming invasion to be impossible) and the limited need for emergency logistics in the time horizon of two years after the last vaccination. Altogether it is striking that the risk for control outcome due to the inherent low-level persistence of rabies actually reaches zero within a finite time interval.

CONCLUSIONS

Finally we translate the three results shown above into applied statements:
1. The role of rabid foxes for the formation of the typical spatial rabies pattern overestimated and particularly emergency measures should be based on the interaction of diffusive short-distance transmission and rare long-distance transmission events during the time span of dispersal.
2. Small. randomly distributed (i.e. highly fragmented) errors in the vaccination of fox populations (by random wind shift or bait disruption) are insignificant and instead favour the eradication of rabies.
3. A long-term, large-scale vaccination programme can be conclusively proven to have failed or succeeded at least two years after the last baiting campaign.

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