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Scenario-analysis Evaluating Emergency Strategies after Rabies Re-introduction

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Abstract: Now that the elimination of rabies in Western Europe is nearly complete, thanks to the oral mass vaccination of foxes (ORV) which took place over the last 25 years, it is necessary to prepare for emergency situations due to the re-introduction of rabies from still infected areas. Such emergency strategies should aim at minimizing the risk of falling back to large-scale vaccination, in a cost efficient manner.

An approved spatially-explicit simulation model of spread and control of rabies was adapted to the new problem of re-introduction of rabies into free areas. The logic of the model and options for local emergency vaccination (for example ring-vaccination vs. compact area treatment or heavily concentrated vs. thin extended control areas) were determined. Based on systematic simulation experiments the performance of strategic options was assessed.

Key issues such as public health risk (i.e. number of rabies cases), failure risk (i.e. disease breakout from the control area), and budgetary risk (i.e. duration of the emergency program) were simultaneously considered. The results obtained reveal efficiency relations that contradict *a priori* derived management suggestions.

INTRODUCTION

Rabies is life-threatening for humans and the most important viral zoonosis from a global perspective. In Europe and North-America, wildlife is the main reservoir (i.e. foxes, raccoon dogs or raccoons). In areas with re-occurring rabies epizootics, oral mass vaccination (ORV) has proven to be efficacious, cost-effective, and acceptable by the public. The long-term and large-scale oral vaccination of wildlife eliminated rabies at the regional level in Central Europe and the Americas. Consequently, repeated vaccination in these regions has ended and, eventually, its host populations will be completely susceptible to new rabies infection.

Therefore, it is necessary to prepare for a local outbreak in non-immunised wildlife populations [1]. Revitalising country-wide vaccination appears to not be well adapted to the detection of a local rabies outbreak [2]. A WHO recommendation suggests 5,000 km2 of compact vaccination area as the minimum sustainable strategy [3], but there are no details regarding the plausible spatial configuration. Field practice demonstrates that the modern aerial distribution of vaccine baits performs precisely, even with complex spatial distribution patterns [4]. It appears worthwhile to exploit these techniques to design adjusted contingency plans in the event of rabies re-introduction.

In an emergency the outbreak will be very localised, first putting the surroundings at risk due to successive spatial spread of the infection throughout the host population. Thus the main challenge of local emergency control will be the race between the time it takes to build-up a properly vaccinated population and the distance the disease might have spread in the meantime. Unfortunately, the most appealing strategy against breakouts of infected hosts of the controlled area does not work. Simulations have shown that a ring vaccination, i.e. fencing the epidemic by a ring-shaped area of competently vaccinated hosts at an adequate distance from the detected outbreak, always performs worse than a vaccination protocol that places all the baits in a compact circle centred on the first detected case [5]. In conclusion, the immediate control of a compact area around the detected case is mandatory for an emergency strategy.

However, the main drawback of the ring was identified as the neglected or delayed combat of the disease inside the ring-shaped baiting area [5]. The logical strategic alternative would combine both aspects, the extension of the outer border and the immediate start of controlling the total encircled emergency area. The fixed strategic parameter would thus be the total amount of baits allowed for a campaign in the emergency area, but the extent of the area could be traded against baiting density. The concept is symbolised best by rolling out dough, i.e. the thinner it lays the larger it stretches. Here, the comparative performance of differently rolled out dough is analysed.

An explicit simulation model of the fox-rabies system was used to compare the different bait distribution schemes. The chance of elimination (strategic performance), how long control schemes are needed to control the outbreak (budgetary needs), and the number of rabies cases occurring inside the control area (Public Health) are considered.

MATERIALS AND METHODS

Baiting strategies were evaluated with a model of the rabies-fox system. The model was particularly tailored to support control planning. A spatially-explicit, individual-based, time-discrete modelling approach was applied. The temporal resolution was one week to properly consider the effect of the time of introduction of rabies into the fox population, the time until detection of the epidemic, and the timing of the initial vaccination campaign. The spatial scale corresponds to fox group home-ranges represented by regular grid cells. The rules of rabies dynamics between fox family groups, as well as individual dispersal of juveniles after maturity, were adopted from the literature [6]. Compared to previous rabies models which had addressed an introduction of rabies [7,8] it was necessary to extend the simulation area (i.e. 256 times 256 cells corresponding to ~65.536 km^2 in a Central European scenario) in order to allow for relevant dimensions of the control area. The detailed structure of the model, sources of parameterisation, and validation or sensitivity considerations are as previously described [9].

Basic fox population model

Each cell comprises a family group of age-classified individual foxes (juvenile and adult). Fox groups in the field contain on average 2–3 adults (i.e. 1 male and 1–2 females) before reproduction. In the model this pattern is realised by assuming a maximum group size of five adults together with the mortality and dispersal process. Without rabies, adult foxes have a monthly mortality of 6.1%. Juveniles are subjected to a monthly

mortality of 12% until dispersal. After dispersal they are treated as adults. Reproduction is scheduled in the first week of April. All non-empty cells produce one litter of normally distributed number of cubs with mean 5.5, standard deviation 1.5, and range between 0 and 13. Fox groups which consist of exactly one individual reproduce with 50% probability. This rule accounts for floaters and multiple mating males as well as for non-reproducing females.

With these population dynamics, on average 3.5 juveniles per group emerge in the maturity dispersal (J. Goretzki, pers. comm.). The dispersal occurs for eight weeks from October to November. During this phase, one-eighth of all cells were selected randomly per time-step. Out of each selected cell, all juveniles move consecutively. The dispersing individual was randomly assigned with a main direction from eight neighbour cells which is maintained in each step with 50% probability. In the remaining half of the steps, the individual deviates to the left or to the right by one cell with equal probability (i.e. 25%). The probability of settling in a cell (PSettle) increases with the distance travelled (PSettleDistance), but decreases with the number of adult foxes already in there (CrowdingFactor):

PSettle = PSettleDistance($Step$) x CrowdingFactor($NumberOfAdultFoxes$)
PSettleDistance($Step$) = (15% + (1-0.15) x $Step$/60)
CrowdingFactor($NumberOfAdults$) = $0.5^{(NumberOfAdults)}$ if $0 \leq NumberOfAdults$ < 5; and 0 else

The dispersal of an individual is limited to 100 steps, i.e. a maximum of 100 fox group home-ranges will be passed. During each step a mortality of 2% (adjusted to 22% dispersed foxes found dead) is assumed. Individuals that did not find a home-range after 100 trials die, which actually happens very seldom in the simulations.

Rabies transmission

Each fox has a disease state (susceptible, infected, infectious, or immune). The state is updated weekly. If infection was introduced into a cell by neighbourhood contact, one adult fox is randomly selected. If this fox is not susceptible but "immune," nothing happens; otherwise its state changes from "susceptible" to "infected." The "infected" fox becomes infectious after a negative exponential distribution with a minimum of two weeks and an effective mean of 3.5 weeks. During the following infectious period of one week, a fox can transmit the rabies virus.

An infectious fox passes the virus on to all other susceptible foxes within the cell. If there is at least one infected fox in a cell, then the eight neighbouring cells have a probability P_{inf} of becoming infected. During mating period (January and February) any neighbouring cell within a distance of up to three cells will be infected with decreasing probability of P_{inf}^1, P_{inf}^2 and P_{inf}^3. There are hardly any infections during dispersal. However, juvenile foxes dispersing in their incubation period will cause standard transmission after settlement [10].

Distribution of baits

Standard vaccination protocol on the regional scale comprises biannual campaigns with 18–20 baits distributed per km^2. Two vaccination events are performed in the model: one in the first week of April and one in the second week of September. Grid cells represent the spatial equivalent of home-ranges of fox families, which do not have an equal area size and hence will not receive an equal number of baits [4]. This non-equal assignment of bait pieces approximates spatial fox group home-ranges and was based on simulations of standard aerial delivery [11]. The baits randomly drawn to fall into a fox group home-range are assumed to be lost with 80% probability due to competitors, and considering baits unfound or only partly consumed. The baits remaining in a particular cell are distributed randomly to the respective individuals, independent of their state. The "susceptible" foxes become permanently "immune" two weeks after receiving at least one piece of bait. With these rules, the immunisation level nearly saturates after two campaigns [12].

Emergency vaccination

The middle cell of the grid receives an external infection during a randomly chosen week of the year. Subsequently, any infected fox could be the first detected, with a probability of 2% [13]. Rabid juvenile foxes will be detected only from dispersal onwards. After first detection, a preparation time of two months passes until the first vaccination campaign can logistically be undertaken (A.Vos, personal communication). Further campaigns are scheduled according to the standard protocol: in the autumn and spring, with the only exception being that the second campaign will not be undertaken less than two months after the initial baiting. The emergency area is always centred on the first detected rabies case, ignoring other "infected" cells on the grid.

Simulation experiment

Simulations are performed on a grid of 256 × 256 cells, which totals 65,536 cells. After the initial vaccination campaign, simulation was performed for a further six years, i.e. in total 13 campaigns were evaluated. Each simulation scenario was run 10,000 times to cover stochastic effects. The vaccinated area is compact around the detected outbreak and implemented in the model as a solid square. Three different amounts of baiting resources are considered available immediately after detection: 128,000; 200,000; and 320,000. In the reference situation, if 20 baits are distributed per km^2 and mean cell size associates with 1 km^2, then these baits correspond to a control area of 6,400, 10,000 and 16,000 km^2, (i.e. either 80 x 80, 100 x 100 or 126 x 126 cells). The output is measured as the proportion of runs per scenario that failed i.e. ended in a transmission event outside the vaccinated area; the length of the time span until success (more than 13 campaigns was handled as failure); and the cumulative number of infected foxes in a run.

For each amount of baits the simulation experiment is performed by increasing baiting density from five to 40 baits per km^2 (i.e. 5, 6, 7, 10, 15, 20, 25, 30, 35, 40). As the total amount of distributed baits was kept constant throughout the simulation experiment, the vaccination area shrinks accordingly. For the example of 200,000 baits, the vaccination area is reduced from 40,000 to 4,900 cells.
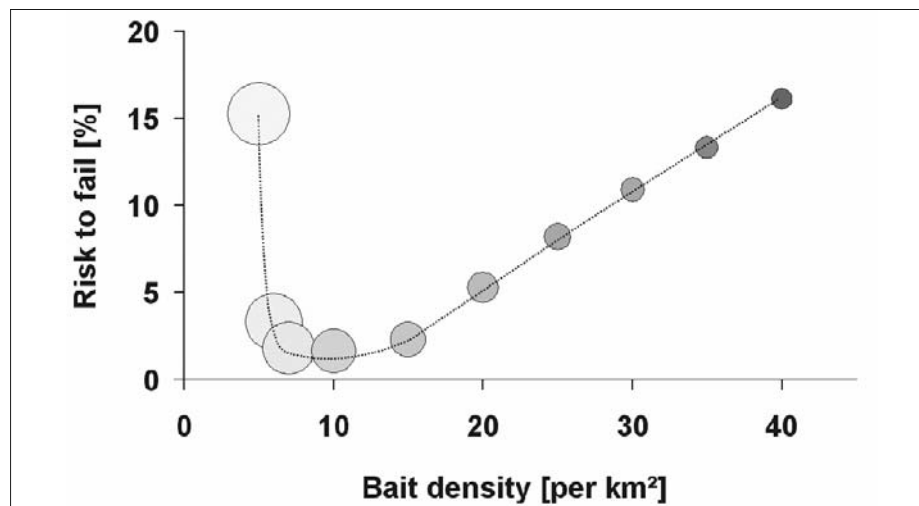

Fig.1: Relation between baiting scheme and risk of failure, i.e. ending up with rabies detection outside the control area out of 10,000 repetitions. The graph depicts the result exemplified by the values for the intermediary resource level (i.e. 200,000 baits). Circle diameter represents the size of the vaccinated area dependent on the applied baiting density. Assuming approximate Central European fox densities, the circle area represents 40,000 to 4,900 km^2. As long as the amount of distributed baits suffices to properly vaccinate foxes, reduced baiting density increases the vaccination area and actually reduces the risk of failure of the emergency program. In particular, the standard of 20 baits per km^2 results in a 5% risk of failure. Halving baiting density to 10 b.p.km^2 reduces the risk of breakouts by nearly 70% (i.e. 5.3% vs. 1.6%).

RESULTS

The results are qualitatively equal for all three amounts of baits (Figures show data of the intermediary volume of 200,000 baits). In Fig. 1 the potential to eliminate the outbreak is compiled for the ten distributional schemes. On the bottom axis the effective baiting density in the vaccination area is plotted against the risk of failure, i.e. the proportion of 10,000 runs that ended up in a breakout of the disease from the control area or in disease persistence. The decreasing size of the circles indicates the decrease in vaccinated area. Starting with a high density of 40 baits per km^2

(respectively with a small vaccinated area of 4,900 cells), the risk of failure exceeds 15% (i.e. 16.1%). Increasing the vaccinated area by reducing the baiting density improves the performance of the distributional scheme up to a minimum risk of failure of less then 2% (i.e. 1.6% at 10 baits per km^2). Further enlargement of the vaccinated area does not improve the outcome, which is due to the reduced power of controlling the spread of the disease with very low baiting densities. In case of minor (major) amount of baits i.e. 128,000 (320,000) the risk of failure with small areas resulting from 40 baits per km^2 was determined as 29% (7.4%) whereas the minimum risk, again for 10 baits per km^2, was found to be 7.5% (0.2%; i.e. for 320,000 baits and hence always relatively large areas; the minimum risk of around 0.2% was found for a range of baiting density between seven and 10 baits per km^2).

Based on the risk of failure associated with a distributional scheme, Fig. 2 depicts two additional performance criteria: time until success (Fig. 2A) and total number of rabies cases (Fig. 2B). As shown in Figure 1, the risk of failure ranges between 1.6% and 16.1% when distributing 200,000 baits. Therefore, more than 84% of all simulated outbreaks were contained successfully by any of the emergency programmes. However, time until successful eradication increases with reduced bait density. The Y axis in Figure 2A shows the number of campaigns performed before the maximum time span required for successful control, or the last control success, occurs in one of the 10,000 repetitions. The measure varies between four campaigns (i.e. bait density beyond 30) and 12 campaigns (i.e. bait density below 10). Short time spans indicate a very quick decision between success or breakout; meaning for example if 35 or 40 baits per km^2 are applied, the outbreak must have been dropped out of the control area after four campaigns (13% or 16.1% respectively) or will be eliminated (87% or 83.9%). Maximum time spans indicate a low power of the strategy to control the outbreak because after any further campaign some (random) events of elimination occurred.

Finally, the number of rabies case per control program (Fig. 2B) increases with decreased baiting density by magnitude of ten. For baiting density beyond 10, the complete range of risk to fail (2.3% to 16.1%) was associated with cumulative rabies cases ranging only between 250 and 500.

DISCUSSION AND CONCLUSIONS

The power to contain and control a local rabies outbreak in a completely susceptible fox population by mass vaccination with limited resources was analysed. Compared to the large-scale application of ORV in the past, the emergency situation is different with respect to a higher disease free population density and the limited vaccinated area. Both differences decrease the chance of success of a control strategy. In contrast, the very few primary infected animals support control efforts due to stochasticity in a small "population" (here infected hosts). Therefore it is comprehensible that results do not provide clear-cut evidence for either improved or worsened performance of local emergency vaccination compared to large-scale control.

Technically, the representation of the emergency control area by a regular circle is an abstraction. When applied to real landscapes such areas are non-regular, as they are usually determined by administrative borders, hence certain excess areas must be baited additionally. The geometric simplification in the simulation study represents the required core area, which must at least be covered by vaccination while the physical extent will be defined along administrative units.
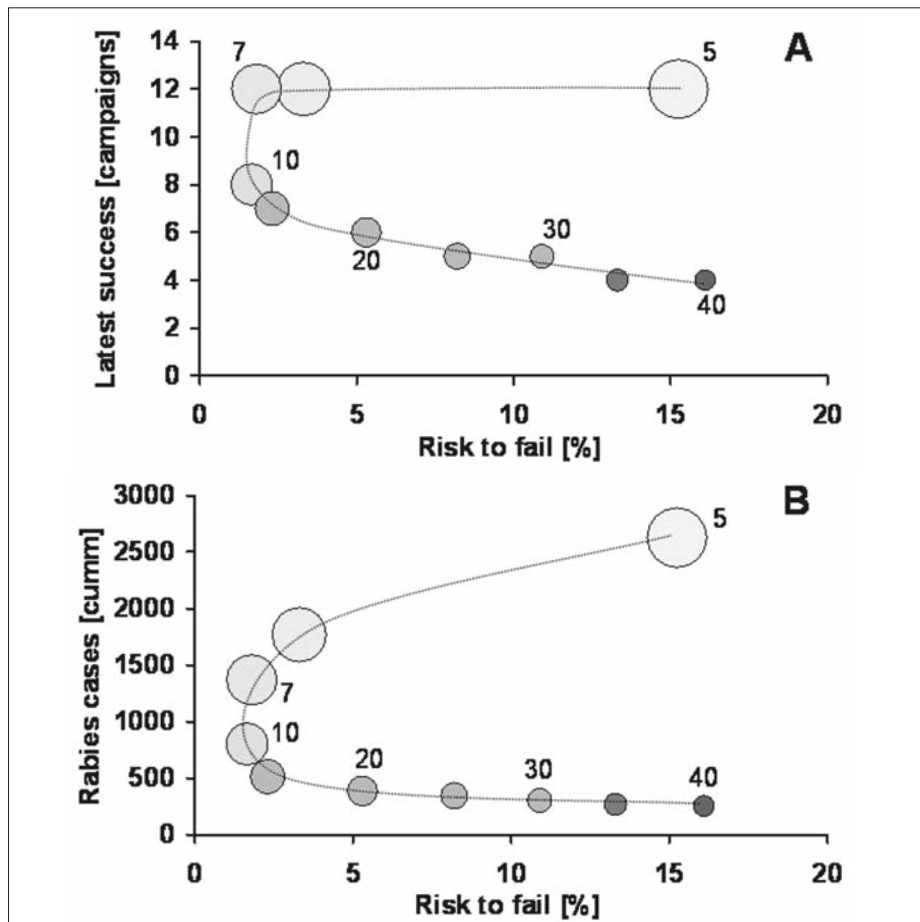
Fig.2: Relation between risk of failure of varying distributional schemes and (A) the number of campaigns until the latest date of eradication occurs out of 10,000 runs; and (B) the total number of rabies cases averaged over 10,000 runs. The graph depicts the result exemplified by the values for the intermediary resource level (i.e. 200,000 baits). Circle diameter represents the size of the vaccinated area dependent on the applied baiting density (labels in diagram). (A) When bait density decreases from 40 to 10 baits per km^2 then the maximum duration of successfully controlled outbreaks doubles from four to eight campaigns. (B) In the range of baiting densities from 10 to 40 baits per km^2 the associated number of rabies cases varies between 800 and 250.

Comparison of different amounts of baits revealed in general that the more resources that can immediately be dedicated to an emergency vaccination campaign the better the chance is to control the outbreak, given the application of the same baiting density. Furthermore, the optimal adjustment of bait density vs. vaccinated area becomes more rewarding the lower the total amount of available resources actually is.

How to adjust bait density vs. vaccinated area for fixed amount of baits? The most obvious implication of the results is that concentrating baiting resources to small, intensively vaccinated, areas is not efficient in improving final success. For

example, the WHO guidance for emergency vaccination recommends an area of about 5,000 km² without further specifications [3]. Copying recent strategic parameters, 35 baits per km² would be applied [14]. Additionally, the realisation of the 5,000 km² could easily approach 5,800 km² due to extensions along natural barriers or administrative borders. This scenario correlates to the second right point in Figure 1 where the simulations predict around an 85% chance of controlling the outbreak. However, if a lower bait density of 15 baits per km² is applied (i.e. a value already known from field application in the epidemic situation) the vaccinated area enlarges to 14,000 km² and the results suggest a remaining risk of failure of only less than 2%. The gain increases the budget due to flight logistics on a tripled area but the required amount of baits, which is the costly part of ORV, remains unchanged.

As long as solely Figure 1 is considered, baiting density at the level of 10 appears to be the preferred strategy. At this value the power to control the outbreak balances insufficiency to contain the spatial spread over the required time. The minimum risk at 10 baits per km² (found for all three amounts of baits) apparently is related to some minimum immunisation level realised inside the vaccination area below which controlling even a local outbreak is no longer practicable. Consequently, strategic alternatives can be selected only from above this baiting density. The conclusion assists analysis of the two other performance criteria: time till success and number of rabies cases (Fig. 2). Larger values of these quantities indicate reduced performance of a potential strategy. The longer the emergency program needs to achieve final results, the more campaigns must be undertaken and the higher the cost. The more rabies cases occur in the fox population, the heavier the exposure of people or pets in the affected area.

The aim of decreasing the risk of failure favours a minimal baiting density (i.e. a maximized control area), but minimisation of total costs of the program as well as Public Health risk seem to argue for the opposite, i.e. an increase of baiting density by shrinking the vaccinated area. Although this situation seems to be a conundrum, more thorough consideration of Figure 2 partly paves the way to a decision. With respect to the Public Health criterion, a wide range of applicable baiting schemes (i.e. from 15 to 40 baits per km²) differed by not more than 250 rabies cases (Fig. 2B). Relative to additional occurrence of rabies after a potential breakout, the gain in a lowered risk of failure should outweigh the slight increase in exposure, at least in rural emergency areas.

With respect to the budget required by increasing the number of necessary campaigns when baiting density is reduced (Fig. 2A), one must account for WHO guidance in declaring a country (or region) rabies free [15] which takes two years (i.e. four campaigns) of continued vaccination after the last detected rabies case. The concentrated application (40 baits per km²) will provide the rabies free status with around 84% probability (Fig. 2A; x-axis at 16% failure) after eight campaigns (four campaigns until final elimination in the latest case of success - Fig. 2A y-axis - plus the additional four campaigns). Alternatively, if baits are distributed at a density of 15/km² then rabies elimination is observed after seven campaigns (Fig. 2A). However, with 15 baits per km² the success rate after four campaigns already approaches 82% (result not shown). Hence, with similar probability, both distributional schemes result in the rabies free status after eight campaigns. However, whilst the concentrated scenario leaves the manager with the remaining 16% certain failures (Fig. 2 A right circle; after four campaigns there was no further elimination result), in the alternative scheme the remaining 18% of emergency controls do not fail.

Indeed, after campaign seven, there is only about a 2% risk of failure remaining meaning that the further 16% are eliminated between campaign four and seven and for these the rabies free status will be achieved after 11 campaigns at the latest. For the strategic choice that reduces the total risk of failure from 16% to 2%, managers have to pay at most for three additional campaigns (i.e. 82% no additional; 14% one; 1% two; and 1% three additional campaigns; result not shown).

The basic understanding of the relationship between baiting density, vaccinated area and control outcome indicates useful decision support. As the next step, the economic dependency between performance measures must be subjected to an in-depth analysis, including a continued emergency after a breakout of the disease from the control area and thus a necessary expansion of the treated region.

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