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The Strength of 70%: Revision of a Standard Threshold of Rabies Control

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Abstract: The success of oral vaccination of foxes (ORV) conceptually is linked to the immunisation of host individuals beyond the herd immunity threshold. However, field evidence and theoretical analysis suggests that mathematically derived values of herd immunity might be rather conservative and, moreover, restrict the adjustment of standard ORV protocols in the case of limited resources. Here, the relationship between baiting effort, duration of ORV programmes and rabies elimination is analysed.

An individual-based, spatially explicit model for the control of rabies in foxes that incorporates the important peculiarities of the vaccination process, i.e. the spatial distribution of infected hosts, irregular home-range use, heterogeneous bait coverage etc., is applied. Using multiple repetitions of simulated ORV programmes, the control outcome is analysed in a chance-like fashion overriding the yes-or-no prediction inherent in the herd immunity concept.

It is shown why control planning must not only aim at particular immunisation levels but, simultaneously, has to specify the allowed time horizon of control success. It is demonstrated that planning a higher chance of elimination increases necessary effort non-linearly. It was found that low immunisation results (i.e. 50%) still provide a reasonable chance of control success. The potential changes in ORV planning and evaluation allowing for the integration of risk concepts in strategies are discussed.

INTRODUCTION

Rabies is still one of the most serious zoonoses in the world [1]. Nevertheless, the combat of wildlife rabies by means of oral vaccination (ORV) represents one of the success stories of disease control. The development of the vaccine and its encapsulation in baits [2], innovative field application [3] and the support of large-scale elimination [4] have resulted in the triumph of disease management methods since the early 1980s. ORV programmes have been conducted in Europe [5], Canada [6], and the United States [7]. After three decades of efficient control, however, cost

is becoming more and more an issue in rabies control [8], particularly with respect to wildlife rabies in huge areas of Eastern Europe, and the resources needed for dog rabies control in Asian countries. Therefore, strategic improvements are necessary and valuable. Although the bait coat, the vaccine, the distribution methods and the overall ORV strategies have been improved with new knowledge gained from field experience and experimental research, there remains an old issue with the strategy: the 70% value of herd immunity, i.e. the minimum proportion of foxes that must be immunised to guarantee the success of ORV.

New insights demonstrate that the standard target of 70% immunised foxes [4] is biased due to modelling techniques applied for its derivation. In [9] the authors show that the estimation of herd immunity using a standard epidemic SIR model was conservative. He found lower herd immunity, i.e. lower by about ten percentage points, independent of the assumed rabies free fox density. The author demonstrates that the classic prediction (i.e. 70%) is due to the omission of spatial processes when representing rabies transmission in the population model. If the rule-based model from distance independent transmission (i.e. perfect mixing of susceptible and infectious foxes no matter how distant they are from each other) is switched to natural contact transmission between spatially neighbouring foxes, then herd immunity is found to be ten percentage points lower (i.e. 60%; Fig. 1).

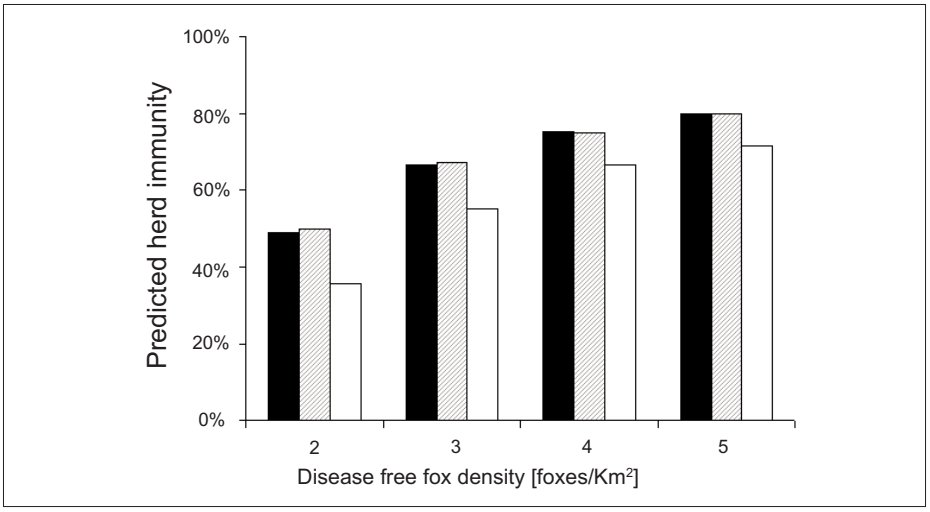

Fig.1: Predicted value of population immunity for increasing disease-free fox density using different models, each with the same population dynamics.
Black bars: historical prediction grounding control target in the past [4]. White bars: improved prediction by the individual-based model with natural local contact transmission. Striped bars: same as before but with perfectly mixing foxes i.e. infected foxes could contact any fox in the population no matter how distant they were from each other ("flying foxes"). Switching from biological foxes (~60%) to flying foxes (~70%) increases herd immunity by around 10 percentage points.

Here, a more detailed analysis of the relation between immunisation level and control outcome over time is presented. Indeed, the theoretically grounded concept of herd immunity provides a yes or no prediction whether a vaccination strategy will succeed in rabies elimination. However, in practice heterogeneities in vaccination

coverage or demographic stochasticity softens the distinctness in outcome. Therefore, insights into the successful control outcome are quantified in a chance-like fashion. The authors' analysis is based on an intensive simulation experiment with the management oriented rabies model that includes a realistic representation of fox biology and rabies epidemiology.

Materials and Methods

Rule-based model

The model is based on the representation of discrete entities. The behaviour of these entities from one time step to the next is described by probability rules from available literature. The dynamics of the model emerges from the entities' behaviour, i.e. from the bottom-up.

The discrete entities of the model are individual foxes and home ranges. Individuals are characterised by state variables such as age (juvenile or adult), the home range they belong to, and their health status (susceptible, incubating, infectious or immune). The home ranges' state variables are their spatial coordinates, the list of foxes comprising the family group using the home range, whether there was any infection in the group in this time-step, and the number of vaccine-filled baits available to the family. The landscape of home-ranges is represented by 256×256 cells with periodic boundary conditions. The extent of a cell corresponds to a fox-family home-range (i.e. approximately 1 km² in Central Europe). The time-step is one week. Within one time-step (ts), the following processes are scheduled: reproduction (first ts of April); natural mortality (each ts); dispersal (October to November); bait delivery (first ts of April and third ts of September); infections (a) within family or by neighbourhood (each ts), (b) during mating (January and February), and (c) after dispersal events (October to November); and update of health status (infectious foxes die, incubating foxes may turn infectious, bait uptake and immunisation of susceptible foxes (each ts)). Bait distribution follows standard aerial design and bait availability is calculated assuming natural home-range assemblages [10;11]. A complete technical description of the applied version of the model has been previously published by Eisinger [12].

Validity

The pattern-orientated approach [13] for validation of the experimental results and qualitative debugging of the model logic was used [14]. Hence, during construction of the model population parameters were repeatedly re-read from the model and compared to equivalent empirical data. The model successfully reproduced fox ecology (e.g. fox densities during the year, or the dispersal distances [15]), the spreading pattern of rabies [16], the development of immunisation levels by a number of campaigns, or the reduction in rabies occurrence by vaccination [17]. After calibrating the unknown transmission, i.e. the probability of infection between groups, the emergent model dynamics were congruent with observations of the fox population in Germany made over the past 40 years including pre-control data, the effect of running ORV, and the situation after eradication. When parameters of the model were altered (i.e. dispersal subroutine, juvenile mortality, home-range structure in the landscape, etc.) results and conclusions did not change.

Simulation experiment

A simulation run was initialized with a stable epidemic situation. The epidemic situation was forced by starting with 100 infected adults and a heterogeneous density distribution. This reliably produced incoherent epidemic waves [16]. After the commencement of vaccination, a biannual scheme (spring, autumn) was maintained for 20 years. The point in time of rabies elimination from the simulation area was recorded. The same run was repeated 10,000 times to balance the stochastic outcome of the simulated control. Finally, the simulation was performed for different levels of average population immunity (48-68%, determined via the strategy parameter of bait density subjected to bait competitors and heterogeneous bait access due to natural home-range assemblages). The probability of elimination (i.e. the respective risk of failure) for different immunisation levels was determined according to the cumulative number of runs with rabies elimination before a given point in time out of 10,000 repetitions. Disease free density was assumed to be three foxes per km² to reflect Central European habitat conditions.

RESULTS

Figure 2 depicts the relation between control time and the immunisation level in a population. During the first two campaigns of a control programme, the immunisation level might be lower (build-up time), but afterwards the value is maintained as the population has already recovered along with advancing elimination. Lines represent isoclines of probability of elimination. Notice that higher probability levels are represented with finer scaling to highlight the interesting levels of nearly complete elimination. Starting with a value of immunisation level (y axis) the cross-points of a virtual horizontal line with the probability isoclines show the devolution of success compared to the effort spent in performed campaigns (x axis). Starting with a (planned) number of campaigns, vertically one reads out the probability of success depending on the immunisation level actually achieved by these campaigns.

Figure 2 highlights the limited value of the threshold criterion of herd immunity. Obviously, and consistent with practical experience, perfect elimination (i.e. 1.00 isocline) does not only depend on an achievable immunisation level but also on control time. Assuming restricted resources (i.e., the number of campaigns possible), the respective pseudo herd immunity to achieve particular goals can be estimated. Using a practical guideline for control planning, the model was asked for the minimum immunisation level required for a 95% chance of eliminating the epidemic within four years; this was found to be 58% (Fig. 2, label a).

A second observation pinpoints the phenomenon of non-linear cost-effect when increased success is required. To eliminate 95% of potential failures requires much less effort relative to the increase of effort necessary to remove the remaining 5%, either by prolonging control programmes or by aiming at a higher immunisation level. For example, take a control programme that realises an immunisation level of 56% with a 90% chance that the epidemic is eliminated after four years (eight campaigns; Fig. 2-label 1). One must budget a further four years (i.e. doubled effort) to expect a 99% success rate (Fig. 2-2), and some 16 years of continued control to be prepared for the worst outcome (i.e. 100% chance; Fig. 2-3). On the other hand, there is already a 50% chance of ending up with elimination after only two years (four campaigns; Fig. 2-4).

If a control programme only suffices to continuously establish 50% population immunisation, then after four years every second programme will already be successful. Continued control for up to eight years will provide success in four out of five trials (i.e. 80%; Fig. 2 label b). The remaining probability of failure is less than 0.2, which means that even after eight years of vaccination, one out of five trials will actually fail to eliminate the disease.

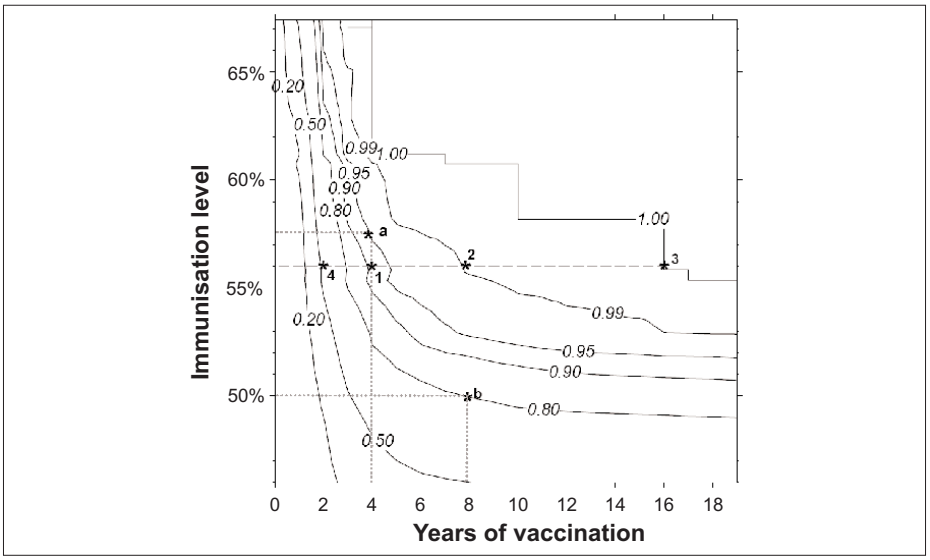

Fig.2: Relation between achieved immunisation level (i.e., the proportion of foxes protected), the number of biannual vaccination campaigns and the chance of rabies elimination.
Label a: According to the management related definition of success, i.e., a 95% chance of rabies elimination within four years, an immunisation level of ~58% averaged over the total population must be achieved by the campaigns. Label b: If control programmes only suffice to continuously establish 50% population immunisation after four years, then every second programme will be successful. Continued control up to eight years will provide success in four out of five trials. The remaining probability of failure is below 0.2 and means that if the mean immunisation level is limited above by 50% even after eight years of vaccination, every fifth trial will fail to eliminate the disease.

Discussion and Conclusions

The established concept of herd immunity referring to the threshold proportion of successfully vaccinated host individuals out of the total target population is based on the characteristics of analytic epidemic models. These tools consider the transmission of infection between host individuals to be like interacting particles. There are two main features inherent in this technique: (1) particles (i.e. infected and susceptible hosts) mix perfectly, and thus any host can simultaneously contact any other individual; and (2) the analysis of such models is not prepared to account for temporal dynamics in the host population because solely the "endpoint" is determined by the model solution.

The first feature, i.e. non-spatial representation, allows host individuals to fly over arbitrary distances even within a day. Consequently, the effect of a spatially clumped distribution of infected animals (as infected from close neighbours) or local low density areas due to acute rabies mortality is excluded from efficacy consideration. This drawback is removed in the model presented here, which explicitly represents individual foxes and thus local contact transmission as well as individual biology. Events are stochastic and the probability distributions always adapted to the actual situation of the host animal with respect to its life history, its disease state and the situation in its perceived surroundings. Nevertheless, model behaviour was analysed

on the population level and results were compared to the predictions of the population-based epidemic model. The technical alignment of both model approaches clearly revealed that the established benchmark of 70% for the immunisation level in European fox populations is conservative, and without loss of generality could be lowered by ten percentage points. Therefore a 60% threshold is suggested to be the more appropriate target [9].

Here, the model is explored to understand the temporal dynamics of a controlled rabies epidemic. Thus in the model vaccination was started in a developed rabies epidemic. Control success was associated with rabies elimination by a single large-scale vaccination programme. Due to stochasticity in vaccination coverage, demography, etc., multiple repetitions of the same vaccination programme provided a spectrum of time till elimination which could be used to determine the time-dependent chance of elimination depending on baiting effort. The latter was transformed into the associated immunisation level achieved in the respective simulation.

The advantage of this study comes from a different view of the relation between control effort and resulting outcome. Traditionally, guided by the herd immunity concept, the control programme has been expected either to succeed or to fail, which is reasonable only in the extremes. Thus, in a population with 100% immunised foxes no vaccination programme can fail. It should also be considered that, depending on host ecology, rabies could die off without any control (i.e., in a small isolated area, or by chance as in the example of dog rabies after WW1 in the UK). Therefore it is not astonishing that multiple repetitions of the same control programme (which actually is possible only in a model) would differ in their outcome. But which realisation should be considered in planning a particular control programme? Because there is no single favourite, a frequency approach was applied to convert uncertainty into decision scheme.

The findings suggest substituting the yes or no view when planning rabies control. In particular, if resources (i.e., the number of campaigns) or baiting efficiency is limited (i.e., the actually achievable immunisation level is less than ideal) a risk of failure of the total programme remains. Even then, estimating the chance of elimination dependent on immunisation level and control time allows for serious management planning.

When can rabies elimination be expected? Obviously the higher the realised immunisation level, the quicker elimination can be expected. In turn, this argues for more baiting effort because rabies roaming longer directly associates to an increased risk for public health. The results presented here, however, reveal a non-linear relation between control effort (here increased immunisation level) and control time. The shorter the control time is, the more effort must be spent on further shortage. For example, in 80% of all trials an immunisation level beyond 66% relates to disease elimination after two years of vaccination while with a 56% immunisation level the same rate is reached after three years of vaccination. Assuming unchanged bait competition rates with higher baiting density, the respective increase in immunisation level by 10 percentage points requires ~45% more baits per campaign [9] where as the reduced control time saves one third of the original resources (10 baits x 3 years = 60 baits per programme with 56% vs. 14 baits x 2 years = 56 baits with 66%). This definitely would support the strategy of shortening control by increasing immunisation level. However, after setting such an ambitious target, realisation is required. Indeed, if in the particular area the calculated amount of baits does not guarantee above a 66% immunisation level, one falls short with the economic benchmarking of the programme. The extensions in control time will be more

expensive due to the higher chosen baiting density. Intuitively, one would argue whether a switch between different baiting densities would allow for hopping between the isoclines. These data are not yet conclusive but preliminary experiments undertaken thus far dash this hope.

The framework of rabies control guidelines allows for the application of these findings to an adaptive strategy of budgeting. Budget allocation can follow insurance models. Assuming a realised immunisation level of 56% or more, there is a 50% risk that the required budget for the control programme will exceed that of two years. Then there is a 20% risk that two years will not suffice the second time (i.e., 50% of runs are longer than two years but only 10% longer than four: 0.1/0.5 = 20%). Finally, a 10% risk remains (1% out of the last 10%) that the budget has to cover more than a further four years. Such time-adapted schemes agree perfectly with the guidelines for achieving the rabies free status of a country. Rabies free status can only be achieved two years after the last case record. By this definition, the final duration of a control programme depends on the field situation two years in the future and thus cannot be planned more precisely in advance (supported by post-hoc analysis of field data; A. Fröhlich unpublished manuscript).

Furthermore, Figure 2 reveals that realised immunisation levels of about 50% have still a potential to finally eliminate the epidemic within a reasonable time frame (i.e. every second trial will succeed within four years). The findings underline that population immunity is not a straight forward criterion for quality assurance of rabies control in the field [18]. Therefore, it appears inappropriate that control campaigns which measured sero-prevalence level of 50% are disqualified (as practised by EU; T. Müller personal communication), although the vaccination programme eliminated rabies from the control area with five campaigns [19].

The principal issue of this study was to demonstrate the variability of solutions one could derive from a more in-depth analysis of temporal dynamics of a controlled disease. Withdrawing the herd immunity concept as the only alternative at hand when deriving an efficient and target-oriented control strategy will pave the way to multi-criteria optimisation taking into account all the aspects at hand: particular evidence (i.e. rabies elimination with less than 60% immunised animals); empirical findings (i.e. rabies elimination with only 15 baits), theoretical suggestions (alternative timing of campaigns), or political demands (i.e. the need for strategies that quickly show results).

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