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# Modelling the effect of landscape heterogeneity on the efficacy of vaccination for wildlife infectious disease control

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## Summary

**1.** Zoonotic disease control presents significant costs and challenges in human and wildlife populations. Although spatial variability and temporal variability in host populations play a significant role influencing the spread and persistence of pathogens, their impact on the effectiveness of disease control are not well understood.

**2.** Field studies are impractical for many zoonotic diseases; thus, simulation modelling is an alternative. Some research has experimented with metapopulation models of host–pathogen systems, with discrete host populations distributed on a network of connections or on a one-dimensional transect of contiguous cells. Little attention has been paid to treating geographic space as a fine-grained two-dimensional continuum, a more appropriate spatial model for many generalist host and vector species.

**3.** Using raccoon rabies as an example, we apply an individual-based spatially explicit stochastic simulation model to evaluate effectiveness of vaccination barrier strategies to control rabies. Barrier width and immunization levels are varied over landscapes with habitats of varying quality and spatial heterogeneity, resulting in varying degrees of host connectivity.

**4.** Our results demonstrate that spatial heterogeneity in the landscape does affect vaccination efficacy. The probability that rabies will breach a vaccination barrier is greater and rabies incidence is higher in landscapes with (i) overall good-quality homogeneous habitat and (ii) overall poor-quality habitat with high spatial heterogeneity, than in landscapes with overall good-quality habitat and high spatial heterogeneity. The influence of landscape conditions on disease dynamics decreases with increasing population immunity.

**5.** *Synthesis and applications*. Using a spatially explicit stochastic simulation model, we demonstrated that landscape spatial heterogeneity and vaccination control will interact to influence the success of controlling infectious disease outbreaks. Further, under some landscape conditions, insufficient vaccination is counter-productive because immunized individuals (i) reduce the number of disease transmitting contacts, preventing the disease from growing rapidly thus depleting the susceptible population; and (ii) survive to replenish the stock of susceptible animals through reproduction, facilitating disease persistence.

**Key-words:** disease spread, habitat connectivity, habitat quality, individual-based model, raccoon rabies, spatially explicit simulation, vaccination

## Introduction

Wildlife diseases pose significant threats to human health. Jones *et al*. (2008) indicate that, from 1940 to 2004, 60% of emerging infectious diseases had zoonotic origins with 72% originating in wildlife. Pathogens of wildlife origin

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also have been responsible for substantial economic costs in domestic animals [e.g. cattle infected by brucellosis from wild elk (Beja-Pereira *et al.* 2009) and tuberculosis from badgers (Donnelly *et al.* 2007)]. Diseases often pose significant threats to the persistence of endangered wildlife populations [e.g. Tasmanian devil facial tumours (McCallum 2005)] and to the economic values of harvested wildlife populations [e.g. chronic wasting disease in cervids (Joly *et al.* 2009)]. Control of pathogens in wild populations is often the most efficient public and animal health protection strategy.

Infectious disease control strategies include host population reduction through hunting, trapping, poisoning, fertility control, introduction of disease and competing species, host population redistribution by habitat alteration, and host species vaccination. Our model system is the ongoing oral vaccination rabies control programmes in terrestrial mammals in North America (MacInnes *et al.* 2001; Slate *et al.* 2009; Boyer *et al.* 2011). We focus on the design of efficient vaccination control strategies, especially the use of vaccine as a geographic barrier to disease spread, and how best to adapt those strategies to habitat configurations of the wild host populations.

The influence of spatial and temporal variability in host population distribution and dynamics on the effectiveness and efficiency of disease control strategies has been widely recognized and exploited. Duke-Sylvester, Bolzoni & Real (2011), through deterministic simulation modelling, identified that latitudinal variation in breeding season length has a direct influence on spatial synchrony in rabies incidence, and that understanding such emergent system behaviour should inform the design of efficient disease control strategies and surveillance programmes. Tinline & MacInnes (2004) delineated geographic units in southern Ontario based on synchronicity in reported rabies cases within those units and asynchrony among units. They used the units to plan the timing and location of fox vaccine distribution to optimally allocate the limited resources available for control. This strategy, combined with effective vaccines, baits and delivery systems, was an important aspect of practically eliminating the arctic fox strain of rabies from Southern Ontario, Canada (MacInnes *et al.* 2001). For rabies and other wildlife diseases, the challenge of evaluating the success and efficiency of alternative disease control strategies remains.

Comparing the efficacy of alternative vaccination strategies through field experimentation with adequate control, replication and measurement precision is impractical, and socially and politically unacceptable. Modelling disease–host systems, particularly with models that incorporate a spatial dimension, offers a feasible and acceptable approach to explore and assess disease control scenarios (Riley 2007; Keeling & Danon 2009). Nonspatial models that assume homogeneously mixing host populations have provided significant insights into disease dynamics (Anderson & May 1991; Barlow *et al.* 1997). However, the requirement to improve the cost-effectiveness of control programmes has motivated epidemiologists to consider geography in their models and examine spatially heterogeneous interventions. For many human diseases, a nodal network structure adequately represents spatial mechanisms and effects (Keeling & Eames 2005; Vincenot & Moriya 2011). For many wildlife diseases, however, habitat is an important determinant of the density of susceptible organisms, and it is continuous in both space and quality. Hence, modelling involves trade-offs between computational resources and scale in the sense of 'detail and breadth of boundary' (Rahamandad & Sterman 2008), and between spatial resolution and extent (*sensu* Dungan *et al.* 2002). With decreasing costs of computational resources; however, modelling habitat at a fine spatial resolution at the individual level has become practical (Riley 2007).

Our previous modelling work (Rees *et al.* 2011b) and that of others (Smith & Harris 1991; Lloyd & May 1996; Russell, Real & Smith 2006) have demonstrated that landscape heterogeneity affects the magnitude and spread of pathogens in wildlife populations. Although limited by data demands, empirical studies have supported this claim. To our knowledge, however, few studies have examined the effectiveness of vaccination barriers in two-dimensional landscapes with spatially heterogeneous host habitat quality, and how those effects inform the design and application of vaccination barriers in the face of a spreading pathogen. Here, we use a spatially explicit, individual-based model (IBM), the Ontario Rabies Model (ORM), to explore these questions.

## Materials and methods

### SIMULATION MODEL

We used the Overview, Design concepts and Details (ODD) standard protocol for describing IBMs (Grimm *et al.* 2006, 2010) to describe the ORM.

### OVERVIEW

#### *Purpose*

This model is a tool for understanding factors affecting (i) animal population and infectious disease dynamics and (ii) efficacy of disease control options including vaccination, depopulation and fertility control under various habitat configurations. We used the model with parameters configured for raccoon populations at mid-latitudes susceptible to the raccoon rabies variant. We measured characteristics of rabies spread through an initially disease-free region with six unique landscape configurations. The landscapes differed in average raccoon habitat quality and in spatial pattern of high- and low-quality habitat (Fig. 1). We compared the effectiveness of 16 vaccination barrier strategies, varying in width and population immunity, in rabies spread and in reducing outbreak severity on the various landscape configurations; we also examined the case of no vaccination to serve as a control.

#### *State variables and scales*

The ORM is a spatially explicit individual-based model that has four hierarchical levels of organization: the individual raccoon, the family

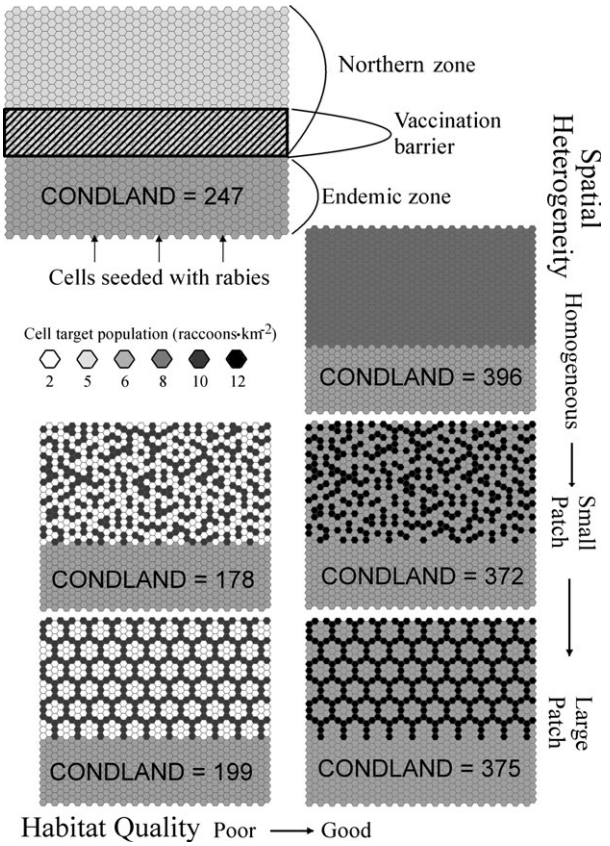


**Fig. 1.** Six experimental landscapes of 40 × 28 hexagonal cells, characterized by the size of the cell target population (ranging from 1·9 to 11·5 raccoons km$^{-2}$). The landscapes differ in the initially disease-free zone as having poor or good overall habitat quality and by the configuration of low-quality habitat cells: homogeneous, small or large patches. Conductance values for the northern disease-free zone with no vaccination are indicated by CONDLAND. Raccoon rabies is seeded in three cells along the southerly extent. The vaccination barrier is placed along the southerly extent of the northern zone.

(mother and dependent offspring), the cell, an area occupied by one or more family groups, and the study area, for which the habitat is specified and fixed throughout a model run. Individuals are characterized, for their lifetime, by identity number, sex, genetic profile and parents' identity numbers; and, for each weekly model time step, by their age, location, dependent offspring identities, disease status (uninfected susceptible, incubating, infectious, immune) and identities of individuals with whom there were disease transmitting interactions. Family groups, identified by dependent offspring identities, affect mortality of dependent young-of-year. Hexagonal cells, with an area of 10·4 km$^2$, are the spatial referencing and accounting units. For any particular model trial, every cell has a carrying capacity, *K*, the average number of animals at week 30 (end of July), supported by the habitat in the cell; it is a direct indicator of habitat quality. The study area, 120 × 97 km$^2$, is composed of a set of spatially contiguous cells (Fig 1).

### *Process overview and scheduling*

Model processes are applied at discrete time steps of 1 week; some processes are applied only 1 week during the year, for example birth pulse at week 18 and others, like mortality, are applied every week, but rates vary according a schedule of age- and sex-specific relative mortality risk. Model processes fall into three groups: demography, disease and control. Demographic events, all stochastically determined, are reproduction, non-disease-related mortality and dispersal. Juvenile and adult animals have the opportunity to breed with age-class-specific probabilities of birthing a litter. Mating occurs between randomly selected male and female pairs concurrently located in the same cell. Each animal is subjected every week to age- and sex-specific mortality risk, the probability of death is modified by the ratio of current cell population to the cell's carrying capacity. No animals survive beyond 8 years. Animals may also die from rabies and from disease control depopulation.

All animals are allowed one opportunity per year to move from the cell in which they are located. Dispersal may occur during an age- and sex-specific range of weeks. Dispersal distances are established stochastically from age- and sex-specific distributions; direction is uniformly random. Dispersal movement occurs within one weekly step, and the animal moves directly to the destination cell without interacting with animals within intervening cells.

Each week, every individual incubating the disease is given a chance to move into the infectious state, according to a probability distribution of incubation periods estimated from field studies. Every infectious individual has an opportunity to infect every susceptible animal within its current cell and a percentage of the raccoons in each of the adjacent six cells based of the overlap of an animal's activity area between the home cell and the adjacent cell. Of those interactions, a user-defined proportion results in the transfer of the pathogen and the newly infected move into the incubation stage for a user-specified infectious period. This 'transmission probability' was estimated through model calibration (Appendix S1, Supporting Information). In this study, the only disease control process examined was vaccination. Once the cells to be vaccinated were specified, all susceptible individuals in each chosen cell are randomly given a chance to move to the immune state until the specified level of population immunity is achieved.

## DESIGN CONCEPTS

### *Emergence*

Raccoon population levels and the spatial distribution of raccoons in their various disease states over the study area at the resolution of the cell emerge from the processes of reproduction, nondisease and disease mortality, and dispersal, operating on individuals. Similarly, rabies dynamics, indicated by levels and distribution of disease mortality and rates of disease spread, emerge from processes of individual inter-animal disease transmission and infection processes and vaccination operating on the emergent spatial distribution of susceptible host animals. Although not a model response variable *per se,* connectivity for disease spread is an emergent property of any particular spatial configuration of habitat qualities and vaccination strategies. We used surface conductance, defined by circuit theory, as our metric of landscape connectivity. Conductance is a functional metric of landscape connectivity based on the known relationship between circuit resistance, a continuous variable and random-walk commute times, applied in landscape genetics and ecology research (McRae *et al.* 2008; Walpole *et al.* 2012).

### *Fitness*

While individual fitness response to the environment is not modelled explicitly, there is, at the cell level, a dependency of mortality rates on the relationship between individual cell population levels and the habitat carrying capacity for the cell, which implicitly provides a fitness feedback from local population density (Appendix S2, Supporting Information).

### *Individual interactions*

The model simulates interactions between individuals through mating and disease infection. During the mating, males and females within the same cell are paired at random. Offspring remain with their mother until the user-defined age of independence. Disease interactions simulate transmission of rabies from a raccoon in the infectious state to one in the susceptible state. Each week, every infectious animal has the opportunity to infect every animal within the same cell. An infectious animal may infect susceptible animals within its home cell, or within the cell at the end of a dispersal event and a proportion of animals in any of the cells immediately adjacent to these cells (Appendix S1, Supporting Information).

### *Stochasticity*

Reproduction, dispersal, disease and mortality events are all stochastically determined, through random selection from discrete probability distributions, for example litter size, incubation period, barrenness, mortality, dispersal distance and direction.

### *Collectives*

Mother–offspring groups are collectives which function as a unit until the young reach the user-specified age of independence. Maternally dependent young-of-year die if the mother dies. The cells are collectives, in that all animals within a cell at a point in time are subject to the same habitat, mortality rate schedules and disease control effects.

### *Observation*

Observations of the raccoon rabies system are made from an omniscient point of view. While the model maintains the weekly status of every individual animal, we chose to record weekly data on individuals and rabies deaths including their cell location. From these data, we calculated our response variables for each model trial: (i) whether or not rabies breaches a vaccination barrier (a breach occurs when $\geq 1$ rabies cases occurred north of the vaccination barrier) and (ii) total incidence of rabies cases for the first 10 years of an outbreak. The response variables were measured within a reporting area in the northern zone that excluded the two rows of cells on the west, east and north sides of the study area to minimize boundary effects.

## DETAILS

### *Initialization*

We built the model landscape by partitioning the entire study area into hexagonal cells. The modelled landscape (11 637 $km^2$) had two distinct regions: (i) an enzootic zone in the south, $40 \times 10$ cells of uniform and intermediate habitat quality; and (ii) a northern, initially rabies-free zone, $40 \times 18$ cells, the landscape where the quality and spatial configuration of habitat varied and where we applied vaccination (Fig. 1). The value of $K$ in the southern zone of homogeneous habitat was 60 (5·8 raccoons $km^{-2}$) in every cell. The northern landscapes varied by (i) habitat configuration (CON) which may be spatially homogeneous, or contained small or large patches of low habitat quality, and (ii) overall habitat quality (HAB) being poor (mean $K = 53$) or good (mean $K = 85$).

In our experience, for eastern North America, defining low habitat quality patches instead of high-quality patches was more representative of conditions that a generalist species, like raccoons, encounter. For raccoons in rural eastern North America, examples of poor-quality patches include (i) mountain areas (coniferous forest; less access to water; fewer resources from people and agriculture) and (ii) core areas of contiguous forest and of large agricultural fields (forests are better for shelter but poorer for food resources, and agricultural fields are poorer for shelter and better for food resources). In this sense, our configurations of lower-quality patches simulated being surrounded by either valleys or a finer-scale mosaic of forest and agriculture such that food and water resources were richer and there were better opportunities for shelter near those resources. Large patches were hexagonal aggregations of seven contiguous cells separated from each other by 1 cell width of high-quality habitat. Small patches were individual cells randomly distributed. In both cases, the configuration consisted of 420 low- and 300 high-quality cells. The homogeneous configuration served as experimental control for assessing the effect of the small and large patch habitat configurations on rabies dynamics. Landscapes with low overall habitat quality had patches with target densities of 1·9 raccoons $km^{-2}$ ($K = 20$), surrounded by cells with target densities of 9·6 raccoons $km^{-2}$ ($K = 100$). Landscapes with high overall habitat quality had patches with target densities of 5·8 raccoons $km^{-2}$ ($K = 60$), bordered by target densities of 11·5 raccoons $km^{-2}$ ($K = 120$). These values of $K$ mimicked raccoon densities for landscape conditions in eastern North America where raccoon rabies is endemic. These choices of $K$ also allowed us to keep the population size consistent among landscapes of similar quality and focus on the effects of landscape structure rather than population differences, although the different ratios of low-to-high $K$ between the poor and good habitats may be a confounding factor in our study design.

For each landscape configuration, an animal starting population was grown from a single mating pair to the point where population growth stabilized; a period of 100 model years was sufficient to achieve stability. These populations constituted starting populations for experimental trials with varying vaccination strategies. For each simulation trial, we ran the model another 10 years prior to introducing rabies to ensure that the stochastic population processes in the ORM produced a unique starting population for each of 100 trials for each landscape and vaccination strategy.

### *Input*

Values for population and disease dynamics input parameters (Table 1) were primarily drawn from empirical scientific studies for the mid-latitude eastern North American raccoon and rabies

**Table 1.** Overview of the Ontario Rabies Model processes, parameters and their default values

| Definition and unit | Value |
|---|---|
| Biological parameters | |
| *K*: Carrying capacity at week 30 (end of July) | 20, 60, 100 and 120 raccoons per cell distributed as described in *Initialization* section of text |
| Age of independence when raccoon is accounted as a juvenile and no longer maternally dependent | 20 weeks after birth |
| Age when raccoon moves from juvenile to adult age class | 75 weeks after birth |
| Mean annual mortality by age and gender | For ages (0; 1; 2; 3; 4; 5; 6; 7; 8)<br>Male mortality (0·6; 0·4; 0·3; 0·3; 0·3; 0·6; 0·6; 0·6; 1·0)<br>Female mortality (0·6; 0·4; 0·3; 0·3; 0·3; 0·6; 0·6; 0·6; 1·0) |
| Date of mating | Week 9 |
| Date of birthing | Week 18 |
| Prevent mating of siblings | Yes |
| Probability for a juvenile female to successfully mate and produce a litter | 60% |
| Probability for an adult female to successfully mate and produce a litter | 95% |
| Mean litter size | 4 |
| Variance in mean litter size | 1 |
| Percentage of males in a litter | 50% |
| Weeks when dispersal is permitted | Young-of-year Male: weeks 38–43<br>Young-of-year Female: weeks 38–43<br>Juvenile and Adult Male: weeks 8–43<br>Juvenile and Adult Female: weeks 8–15 and 38–43 |
| Dispersal distance (number of cells) distributions by age sex class | For distance (0; 1; 2; 3; 4; 5; 6; 7; 8; $\geq 9$ cells) respective probabilities are:<br>Young of year Males (75·1; 12·9; 6·5; 1·8; 0·9; 0·9; 0·92; 0; 1; 0);<br>Young of year Females: (90·8; 4·07; 1·4; 0·3; 0·7; 0·3; 1·02; 0; 1; 0);<br>Juvenile and Adult Male (88·9; 4·25; 2·6; 0·9; 0·7; 0·9; 0; 1; 1; 0);<br>Juvenile and Adult Female (92·3; 3·06; 1; 0·9; 0·4; 0·7; 0·73; 0; 0; 0) |
| Chance of interacting with animals in 6 neighbouring cells (Appendix S1, Supporting Information) | 22·2% distributed equally among adjacent cells |
| Epidemiological parameters | |
| Incubation period: Distribution of rabies incubation periods (weeks between the infection and the onset of infectious period) | After (1; 2; …; >15) weeks of being infected, the probability of being infectious is (0·01; 0·05; 0·05; 0·1; 0·15; 0·2; 0·15; 0·10; 0·05; 0·05; 0·05; 0·02; 0·01; 0·01; 0), respectively |
| Infectious Period: Duration of infectious stage prior to death | 1 week |
| Transmission coefficient: Probability that the virus is transmitted during a contact between an infectious raccoon and a noninfected raccoon (Appendices S1 and S2, Supporting Information) | 3·5% |
| Are infectious raccoons permitted to leave the study area during dispersal? (if not, they stay in the last cell in their dispersal trajectory and may infect raccoons in that cell and adjacent cells) | No |
| Initial infection locations and times | Every other year 5% of animals in three cells evenly distributed on the south edge of the study area are infected with rabies |

system, primarily from Ontario, Canada (Rees *et al*. 2008). Validity and sensitivity analyses demonstrated that the model parameter set was parsimonious and that the model responded to input parameters as expected (Rees *et al*. 2004; Rees 2007; Ludwig *et al*. 2012). Because sensitivity analysis indicated strong disease response to the disease transmission parameter and because this parameter was estimated by a model fitting process similar to Smith *et al*. (2002) rather than from direct empirical evidence, we conducted further experiment-specific sensitivity analyses described in the following statistical analysis section.

Rabies was introduced every other year as an infection of 5% of the animals in each of three cells evenly spaced across the southern boundary of the study area (Fig. 1). Rabies introductions were made at week 20, corresponding to the spring peak in raccoon rabies cases (Jenkins, Perry & Winkler 1988; Guerra *et al*. 2003).

Vaccination strategies were designed to simulate a range of feasible control actions; vaccination was initiated in year 1 and occurred yearly at week 32 (mid-August) as is typical for delivery of oral vaccines at mid-latitudes in North America (Rosatte *et al*. 2001). The vaccination barrier was placed along the northern side of the border between the enzootic and initially disease-free zone (Fig. 1). We constructed barrier widths (WID) of 20, 30, 40 and 50 km and achieved population immunities (IMM) of 20%, 40%, 60% and 80%. The proportion of low- and high-quality habitat cells within the vaccination zone was equal for all barrier widths in the large patch landscapes and approximately equal for the small patch landscapes given the random distribution of 1-cell patches.

### STATISTICAL ANALYSIS

We used the ORM to generate data from which we computed the two response variables for each trial, whether there was a breach of the vaccination barrier, and total rabies cases over the first 10 years of the trial for 17 disease control strategies. To capture stochastic variation in model outcomes, we ran each experimental parameter set 100 times (i.e. 17 strategies × 6 landscapes × 100 trials). To assess the sensitivity of our results to the disease transmission parameter, we ran the same experimental vaccination and landscape parameter sets and trials with transmission probabilities set at half (low) and double (high) the best fitted estimate of transmission probability (medium). All ORM simulations were run in a Linux operating system environment using high-performance computing facilities (http://rqchp.ca).

We assessed the efficacy of vaccination control strategies (WID, IMM), given landscape quality and spatial heterogeneity (HAB, CON). We computed the proportion of breaches for each combination of the explanatory variables and assessed the effect of the explanatory variables on the frequency of breaches using a classification tree analysis (Breiman, Friedman & Olshen 1984; RPART package in R; www.r-project.org). Classification tree analysis is a nonparametric method that recursively splits the data into increasingly homogeneous nodes. The resulting tree can be interpreted as a series of decision rules describing a hierarchy in the importance of the explanatory variables. We based the decision to split the data using the Gini index to measure the purity of classification within nodes (i.e. breach or no breach). To reduce over-fitting, we used tenfold cross-validation to create multiple optimal tree sizes and selected a final tree having a size that was within one standard error of the minimum cross-validation error. A classification tree approach enabled us to analyse data that were infeasible to process in a logistic regression framework because there was insufficient variation in model outcomes (i.e. many vaccination strategies resulted in 100% breaches or nonbreaches). We used general linear models (GLM) with a Gaussian link function to assess landscape and disease control factors affecting the total incidence of rabies over the first 10 years of a rabies outbreak.

In addition to assessing effects of categorical variables (i.e. IMM, WID, CON, HAB), we included a continuously distributed landscape connectivity variable computed from the maps of the habitat configurations and vaccination strategies. We calculated landscape conductance for disease using CIRCUITSCAPE software (http://www.circuitscape.org; McRae *et al.* 2008) for landscape configuration effects alone (CONDLAND), for vaccination alone on homogeneous landscapes (CONDVAC) and for combined habitat and vaccination effects (COND; Appendix S3, Supporting Information for conductance estimation parameters and resulting values). The connectivity measures were standardized and centred for the GLM analyses.

Our candidate *a priori* set of statistical models increased in complexity from one predictor (i.e. COND, CONDLAND, CONDVAC, CON, HAB, IMM or WID) to multivariable models of the categorical and continuous predictors including interaction effects. To avoid collinearity, the conductance variables were not included in models with the related categorical predictors (e.g. CONDLAND was never included with CON or HAB). We also included second- and third-order polynomials of the connectivity predictors given our expectation of nonlinear relationships with the response variables.

The *a priori* set of models were assessed using Akaike Information Criterion (AIC) techniques (Burnham & Anderson 2002). For each model, we report AIC and the difference in AIC from the top-ranked model (ΔAIC). Models with ΔAIC of 2 or less have effectively equal support (Burnham & Anderson 2002). We assessed the residuals of the top models for heteroscedasticity and nonnormality. Model robustness was evaluating by checking for agreement in the beta coefficients with the same model trial using a robust regression approach (RLM package in R; www.r-project.org).

We planned to use a random effects mixed model GLM to analyse the outcomes of all trials. However, we found the distributions of the total incidence deviated far from normality, which made statistical estimation and inference with a mixed-effects model difficult. Therefore, total rabies cases response variables were modelled in two summary forms: as the mean and the median for each experimental parameter set (100 trials per set). This approach allowed us to focus the analysis on predictors that could explain the variation in outcomes among parameter sets. We selected our final models for interpreting the predictors using the response variable (mean or median) that was most consistent with the parametric assumptions of GLMs with a Gaussian link function. We visually inspected the model residuals by plotting them against all explanatory variables and fitted values for violations of normality and heteroscedasticity. These model-selection analyses were repeated for low and high values of the disease transmission parameter. Predictors in the selected best models under the three disease transmission values were compared to assess the sensitivity of simulation model results and our conclusion to variation in this parameter.

## Results

The classification tree correctly classified 97·5% of the breach outcomes (Fig. 2). Achieved population immunity was the top-ranked explanatory variable for predicting the occurrence of a breach. When IMM $\geq$ 60% (Fig. 2 left branch), the probability of breaching the barrier was 0·41, compared with 0·95 when IMM $\leq$ 40% (Fig. 2 right branch). Following the left branch of Fig. 2, the next most important variable was vaccination barrier width. Low barrier widths (WID $\leq$ 20 km) led to a breach with a probability of 0·92. Breaches still occur at higher barrier widths but again IMM was the more important explanatory variable for breaching. At IMM = 60%, habitat quality finally showed up as an explanatory variable. Following the right branch of Fig. 2, the probability of a breach was 1·0 when IMM $\leq$ 20%. For IMM of 40%, the probability of breach depended first on habitat configuration, then habitat quality and, finally, barrier width.

The assumptions for parametric modelling were best met in modelling total number of rabies cases as a median. Top-ranked AIC models are shown in Table 2; additional models depicted in Table 2 are provided to show how other *a priori* models compare with the 10 top-ranked models. The beta coefficients for the top model are listed in Table 3. Increasing population immunity reduced the total number of rabies cases. Increasing vaccination barrier width also reduced the number of rabies cases. As expected good-quality habitat produced more rabies cases. As landscape heterogeneity increased in grain size (i.e. CON: homogeneous >small > large patches), the number of rabies cases increased. The interaction of habitat quality and landscape

heterogeneity (HAB × CON), however, reduced cases on high-quality habitat with large patch landscapes having the most effect. Finally, our analysis revealed interactions between vaccination strategies and the landscape characteristics that were strongest for achieved population immunity and habitat quality (IMM × HAB). The effects of IMM × HAB indicated that vaccination levels 60% or less were counter-productive in high-quality landscapes (Fig. 3) producing more cases than if no vaccination were used. In high-quality habitats, only high levels of population immunity were effective in reducing cases (IMM = 80%).

Sensitivity analysis of disease transmission probability demonstrated that model results for medium and high transmission values were similar. The top model for the medium transmission value was also a top model for the high value (i.e. $\leq 2$ ΔAIC; Table S1, Supporting Information), and the direction of predictor effects was the same (Table S2, Supporting Information). The top-ranked model at the low transmission value was similar to the top-ranked model at the medium transmission. The low transmission probability model included an additional interaction (IMM × CON) and lacked the main effect for vaccination barrier width (WID). At a low transmission probability, variation in the total number of rabies cases was more sensitive to landscape factors. This is expected because more interactions are needed for the disease to spread, which means that landscapes impeding interactions have a stronger effect on disease transmission and, therefore, the total number of rabies cases. The directions of the variable effects of the low transmission value model were the same as for the model derived from the medium transmission probability (Table S3, Supporting Information). Therefore, we find that, although our model outputs are sensitive to transmission rate, the trends and interpretation of factors affecting the outcomes are robust.

## Discussion

Large-scale oral vaccination of wildlife can be a cost-effective method for managing infectious disease over 1000s of square kilometres (Shwiff, Kirkpatrick & Sterner 2008). However, very little is known about the effect of the spatial variation in habitat quality and vaccination strategy on local densities of individuals susceptible to the

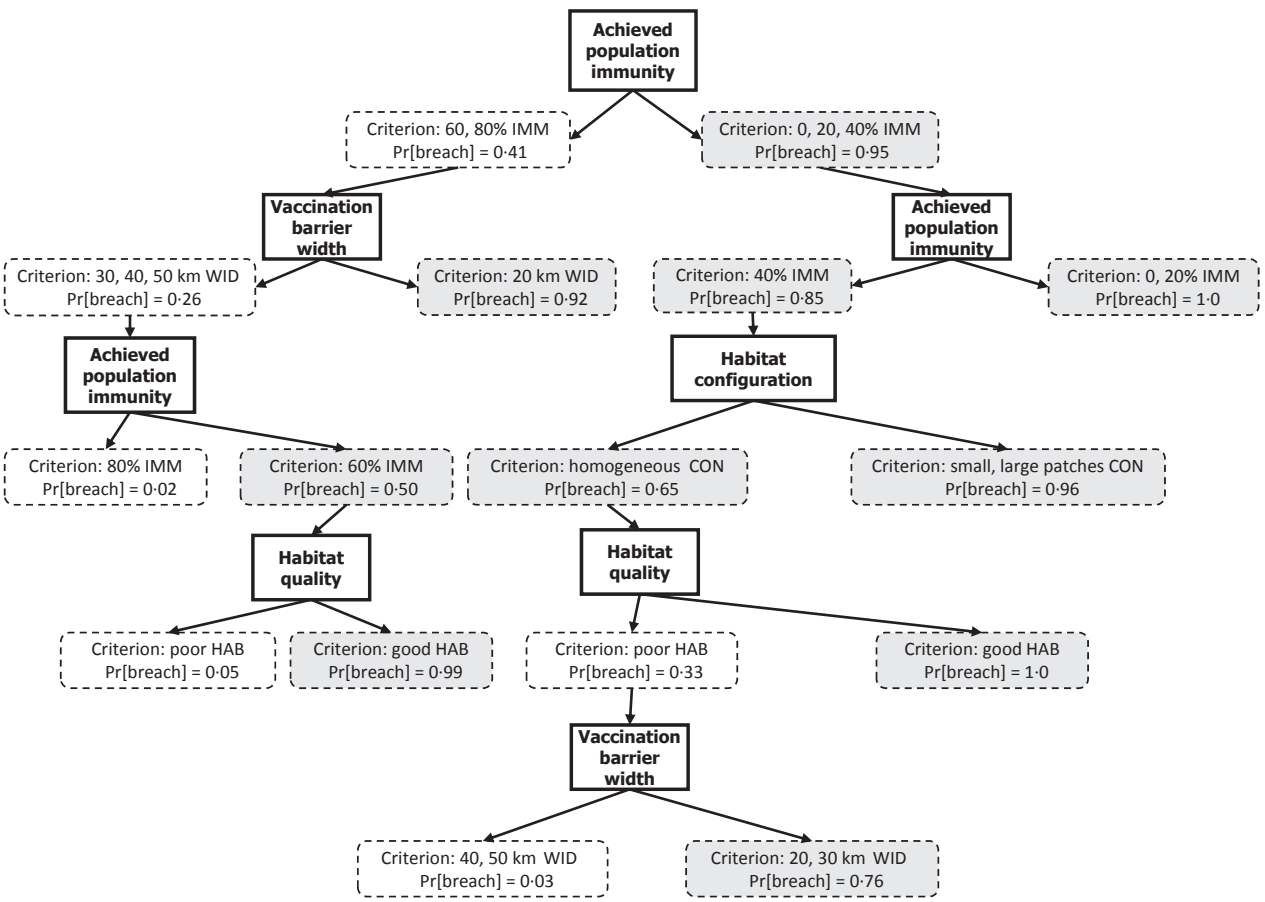


**Fig. 2.** Optimal classification tree for conditions influencing the probability of rabies breaching the northern boundary of a vaccination barrier. Square nodes structure the hierarchy of explanatory variables influencing breach occurrence given: achieved population immunity (IMM), vaccination barrier width (WID), overall habitat quality (HAB) and habitat configuration of low habitat quality landscape cells (CON). The decision rule upon which data are split from a node is defined within round hatched boxes, which show the split criterion, and the probability of the model trial resulting in rabies breach (Pr[breach]); grey shading indicates Pr[breach] $\geq$ 0·50.

**Table 2.** The top 10 AIC ranked models, and five additional models predicting the median of the total number of rabies cases during the first 10 years of an outbreak for the experimental parameter set for given achieved population immunity (IMM), vaccination barrier width (WID), landscape configuration (CON), habitat quality (HAB) and the connectivity measures accounting for the types of disease control (CONDVAC) and landscape (CONLAND), and both of these latter two factors (COND)

| Model | Predictors | AIC | ΔAIC |
|---|---|---|---|
| m18 | IMM + HAB + WID + CON + CON:HAB + IMM:HAB | 100·49 | 0·0 |
| m13 | IMM + HAB + CON + IMM:HAB + IMM:CON + CON:HAB | 104·85 | 4·4 |
| m11 | IMM + HAB + CON + IMM:HAB + CON:HAB | 112·52 | 12·0 |
| m22 | IMM + HAB + WID + CON + IMM:HAB | 125·08 | 24·6 |
| m24 | IMM + HAB + WID + CON + IMM:HAB + WID:HAB | 129·22 | 28·7 |
| m12 | IMM + HAB + CON + IMM:HAB + IMM:CON | 130·66 | 30·2 |
| m10 | IMM + HAB + CON + IMM:HAB | 133·51 | 33·0 |
| m23 | IMM + HAB + WID + CON + IMM:HAB + WID:CON | 137·05 | 36·6 |
| m27 | IMM + HAB + WID + IMM:HAB | 152·59 | 52·1 |
| m28 | IMM + HAB + WID + IMM:HAB + WID:HAB | 157·16 | 56·7 |
| Additional models | | | |
| m15 | IMM + HAB + WID + CON | 239·46 | 139·0 |
| m35 | CONDLAND + WID + IMM | 282·21 | 181·7 |
| m39 | CONDVAC + HAB + CON | 308·87 | 208·4 |
| m33 | $COND^2$ + COND | 311·96 | 211·5 |
| m32 | COND | 355·54 | 255·0 |

AIC is Akaike's Information Criterion, ΔAIC is relative to the most parsimonious model.

**Table 3.** Parameter estimates (β), standard errors (SE), and 95% confidence intervals (CI; lower, upper) of β for the top ranked Akaike Information Criterion model predicting the median of the total number of rabies cases for during the first 10 years of an outbreak for the experimental parameter set given achieved population immunity (IMM), vaccination barrier width (WID), landscape configuration (CON), habitat quality (HAB); reported in reference no vaccination barrier (0% IMM, 0 km WID), the homogeneous landscape CON, and poor overall habitat quality for HAB

| Variable | β | SE | CI (lower, upper) |
|---|---|---|---|
| IMM 20% | −0·54 | 0·14 | −0·82, −0·27 |
| IMM 40% | −1·99 | 0·14 | −2·26, −1·71 |
| IMM 60% | −3·62 | 0·14 | −3·89, −3·35 |
| IMM 80% | −4·57 | 0·14 | −4·85, −4·30 |
| HAB high | 1·18 | 0·17 | 0·86, 1·51 |
| WID 30 km | −0·16 | 0·09 | −0·33, 0·02 |
| WID 40 km | −0·30 | 0·09 | −0·47, −0·12 |
| WID 50 km | −0·32 | 0·09 | −0·49, −0·15 |
| CON small patch | 0·64 | 0·11 | 0·42, 0·85 |
| CON large patch | 0·85 | 0·11 | 0·63, 1·06 |
| HAB high × CON small patch | −0·57 | 0·15 | −0·87, −0·27 |
| HAB high × CON large patch | −0·78 | 0·15 | −1·08, −0·48 |
| IMM 20% × HAB high | 0·57 | 0·20 | 0·18, 0·95 |
| IMM 40% × HAB high | 1·92 | 0·20 | 1·53, 2·31 |
| IMM 60% × HAB high | 2·35 | 0·20 | 1·96, 2·74 |
| IMM 80% × HAB high | 0·20 | 0·20 | −0·19, 0·58 |
| Intercept | 9·36 | 0·13 | 9·11, 9·62 |

disease, and thus, the impact of these factors on disease control efficacy. This lack of knowledge is largely due to the practical limitations of running field experiments over large geographic extents with adequate replication. Advances in computer modelling make this type of experimentation feasible in simulated environments. Using a spatially explicit stochastic simulation model, we found evidence that landscape characteristics and vaccination strategies interact to influence the success of controlling a wildlife-borne contagious disease.

The goal of population-level vaccination is to immunize a sufficient proportion of the population so that the disease cannot become established, persist and spread. The effectiveness of vaccination in the absence of spatial effects has been well established (Coyne, Smith & McAllister 1989; Anderson & May 1991; Barlow *et al.* 1997). As expected, we found that for our homogeneous landscapes, increasing vaccination effort through higher achieved immunity and increasing barrier width reduced rabies incidence. On the other hand, our experiments support previous work (Asano *et al.* 2008; Beyer *et al.* 2011) that the heterogeneous distribution of hosts in space notably confounds the efficacy of vaccination.

Enzootic disease persistence requires a sufficient supply of susceptible hosts, which in turn depends on the rates of host birth, death, immigration and emigration. Landscape heterogeneity influences population dynamics. Hosts prefer or avoid, and have greater or lesser fitness, in certain landscape conditions, and this can influence their movements and the spatial distribution of their population. Landscape heterogeneity influencing the spatial variation in host density also influences the spread and persistence of their pathogens (McCallum & Dobson 2002; Wheeler & Waller 2008). Raccoon rabies incidence is lower or undetected in avoided habitats such as mountains, monoculture pine plantations and is higher in preferred habitats such as urban and mixed agricultural areas (Houle *et al.* 2011; Recuenco, Blanton & Rupprecht 2012; Rees *et al.* 2011a). Landscape conditions can influence host population dynamics, resulting in a range of epizootiological outcomes: (i) die-out, in which too few individuals become infected for the disease to establish itself within the population and persist, (ii) persistence, in which the disease

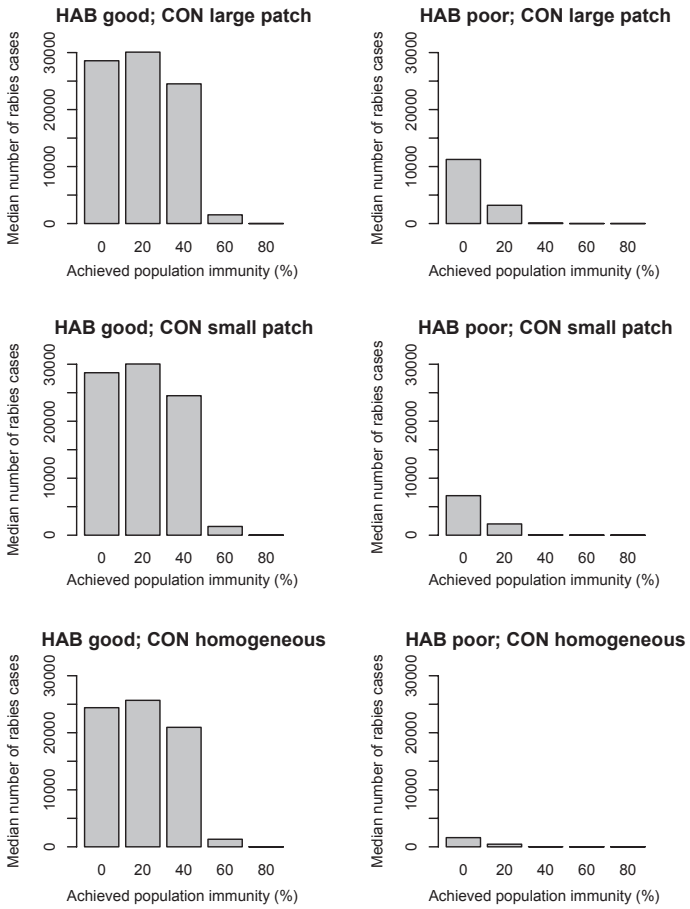


**Fig. 3.** The interaction between habitat quality (HAB) and achieved population immunity (IMM) on landscapes with a large patch or homogeneous spatial heterogeneity (CON) for the median number of rabies cases, calculated over the first 10 years of a rabies outbreak.

becomes enzootic, and (iii) burn-out, in which disease incidence grows and spreads rapidly reducing the susceptible host population below a density that can support disease persistence given host reproductive and immigration rates.

We demonstrated that the interaction of achieved population immunity with different landscape conditions can change the epizootiological outcome from that expected. This was most evident in large patch landscapes with overall poor-quality habitat. Vaccinations at low and intermediate levels of immunity were counter-productive, much as observed by Smith & Harris (1991) in their simulation modelling of fox rabies in British urban centres. Our modelling shows the outcome shifted from burn-out to disease persistence. In these circumstances, immunized individuals reduced the number of effective disease transmitting contacts, preventing the number of cases from growing rapidly enough to 'burn out' remaining susceptible individuals. This left sufficient numbers to reproduce and for the disease to persist. Hartvigsen *et al*. (2007) also noted that insufficient vaccination prolonged epidemics in highly clustered networks of hosts. These situations suggest the potential benefit of using fertility control agents to suppress the production of new susceptible animals to limit persistence. In our study, it was only when the highest levels of vaccination immunity (>60%) were used that an epizootic could be prevented, especially in landscapes with overall good-quality habitat and high spatial heterogeneity. When vaccination levels are high enough, the effects of landscape condition on the disease–host dynamics are outweighed by the influence of vaccination (see left branch Fig. 2). This result was also consistent with the modelling of influenza epizootics on different structures of host networks, where, given a high enough vaccination level, network structure did not have an effect on the epizootic (Hartvigsen *et al*. 2007).

Both main and interaction effects of habitat structure and quality (CON, HAB) were included in the top models, which indicates the important effect of these two components of landscape habitat structure on disease outbreak intensity. The coefficients of the interaction of these components indicated that at high habitat quality, the positive effects of patch size on outbreak are effectively nullified. At low overall habitat quality, patch size has an important influence on disease dynamics. The resulting spatial structure of host populations, particularly at relatively low overall population densities, influences the likelihood of disease extinction because of heterogeneity in rates of disease transmission among individuals (Eisinger & Thulke 2008). Park, Gubbins & Gilligan (2001, 2002) found through spatially explicit simulation modelling that pathogens were more likely to become extinct when there was greater synchrony in infection among host population patches. In our study, in landscapes with low overall habitat quality configured in large patches, there were long

corridors of relatively high-quality cells separating the patches (Fig. 1) and these local areas of high density are much more critical for disease intensity in the overall low-quality landscapes. We suspect that under these conditions, hot spots of the disease could form, spread rapidly along the corridors, synchronize and lead to burn-out.

Recognizing that the two habitat components likely influence disease dynamics through connectivity in the host population, we were very interested in how our integrative measure of connectivity based on circuit theory would perform. Such a single measure is appealing, because it offers a more direct measurement of the underlying process of connectivity and a more general descriptor of habitat configuration which might reveal critical thresholds with respect to disease dynamics. If so, it would be convenient for designing effective vaccination strategies. We found, however, that landscape character was better modelled by the categorical variables (HAB, CON). One reason for this is that the connectivity measures had nonlinear relationships with the response variable. Even when including higher-order terms for the conductance variables, which would allow nonlinear relationships to be estimated, the categorical variables more adequately explained the outcome variation.

An important message for wildlife disease managers is that control interventions must be sufficient to convert persistent disease situations to die-out scenarios. Insufficient vaccination effort may result in changing a potential burn-out to persistence. Another important consideration is whether to treat a burn-out scenario. For example, in a peninsular area with limited immigration of susceptible individuals from outside, allowing burn-out might be the most cost-effective response. This decision depends, however, on the cost–benefit trade-off of waiting until burn-out is achieved or implementing a control plan. A no-control decision may be socially or politically unpalatable, especially if the disease threatens public health and an agency must be seen to be actively protecting constituents.

Wildlife disease control programmes are economically and logistically expensive (Sterner 2009). Simulation modelling provides a framework for exploring a wide variety of questions that cannot be explored through field studies. We conclude from our study that public health and resource managers must realize that effectiveness of vaccination depends on the spatial structure of habitat, host density and connectivity. Hence, expectations about success must be tempered with an understanding of these factors, and this knowledge can inform the design of more effective and more efficient infectious disease control programmes.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article.

**Appendix S1.** Disease transmission in the Ontario Rabies Model.

**Appendix S2.** Population regulation via mortality adjustment.

**Appendix S3.** Conductance estimation and values.

**Table S1.** The top Akaike Information Criterion ranked models for low, medium and high rabies transmission rates.

**Table S2.** Model parameter estimates for high rabies transmission rate.

**Table S3.** Model parameter estimates for low rabies transmission rate.