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A priori prediction of disease invasion dynamics in a novel environment

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Directly transmitted infectious diseases spread through wildlife populations as travelling waves away from the sites of original introduction. These waves often become distorted through their interaction with environmental and population heterogeneities and by long-distance translocation of infected individuals. Accurate *a priori* predictions of travelling waves of infection depend upon understanding and quantifying these distorting factors. We assess the effects of anisotropies arising from the orientation of rivers in relation to the direction of disease-front propagation and the damming effect of mountains on disease movement in natural populations. The model successfully predicts the local and large-scale pre-vaccination spread of raccoon rabies through New York State, based on a previous spatially heterogeneous model of raccoon-rabies invasion across the state of Connecticut. Use of this model provides a rare example of *a priori* prediction of an epidemic invasion over a naturally heterogeneous landscape. Model predictions matched to data can also be used to evaluate the most likely points of disease introduction. These results have general implications for predicting future pathogen invasions and evaluating potential containment strategies.

Keywords: spatial epidemics; rabies; disease invasion; emerging infectious diseases; disease population dynamics

1. INTRODUCTION

Predicting the spread of an infectious disease into a new environment depends on understanding the spatio-temporal dynamics of the host–pathogen interaction. While an extensive modelling literature has developed to account for *ex post facto* patterns of disease spread (Mollison 1995; Shigesada & Kawasaki 1997; Grenfell *et al.* 2001; Hudson *et al.* 2002; Smith *et al.* 2002), few models have then been extended to make *a priori* predictions of patterns of emergence and spread into novel geographical regions. We demonstrate the power of an *a posteriori* model of rabies spatial dynamics to predict *a priori* patterns of spread into adjoining geographical regions.

The spread of raccoon rabies across the eastern USA has proven to be a valuable model system for the analysis of spatial dynamics (Wilson *et al.* 1997; Moore 1999; Childs *et al.* 2001; Lucey *et al.* 2002; Smith *et al.* 2002; Waller *et al.* 2003). The natural history of rabies suggests that transmission is primarily local (one animal bites another animal) and that the incubation period is approximately 3–12 weeks. The infectious period usually lasts 7–10 days and is followed by the death of the animal (Rupprecht & Hanlon 1997).

The rabies epidemic that began in the mid-1970s at the Virginia–West Virginia, USA, border was associated with the translocation of a virus variant highly adapted to raccoons and has spread north into Canada and west to Ohio as an irregular wave front (Nettles 1979; Smith *et al.* 1984, 1990, 2002; Jenkins & Winkler 1987; Krebs *et al.* 1992; Wilson *et al.* 1997). In a previous analysis (Smith *et al.* 2002), we focused on constructing a probabilistic interactive network model of rabies spread across the state of Connecticut (CT). Raccoon rabies entered CT in March 1991 and progressed eastward through the state for the next 5 years. We parameterized the spatial model by fitting parameters describing local rates of spread among townships to minimize the overall difference between observed time to first appearance of rabies and the time predicted from model outcomes. Through this minimization technique, we were able to construct an *a posteriori* model of spread that accounted for *ca.* 92% of the spatial variation in time to first appearance over the state (Smith *et al.* 2002).

We apply the rabies-spread model constructed for CT to a new geographical region, the state of New York (NY). Raccoon rabies first appeared in NY in January 1991 in townships along the southern border with Pennsylvania. As the wave front spread north, 5625 laboratory-confirmed cases of raccoon rabies were reported from 754 townships during the first 48 months (C. Trimarchi, personal communication). Each township was assigned a time to rabies arrival relative to January 1991.

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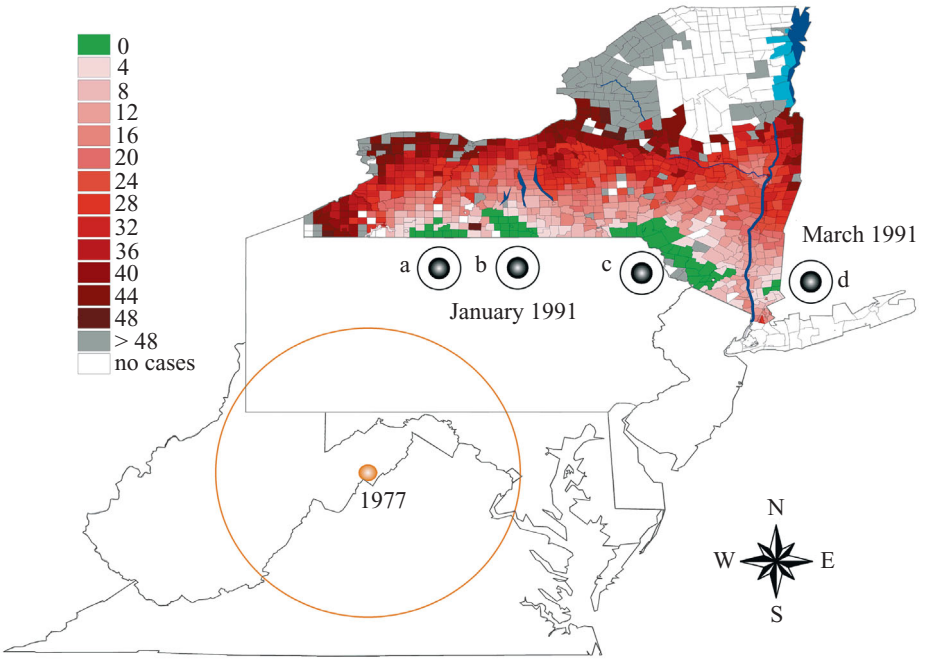

Figure 1. The spread of raccoon rabies across NY townships, indicating time of first appearance (by month) relative to the time of first appearance in New York State (January 1991). Darker colours correspond to greater delays in time to first appearance. The epidemic began along the Virginia–West Virginia border in 1977 (orange dot) and spread as an irregular wave from that point. Circles a, b, c and d show the points where the epidemic entered NY. Townships in light blue are the most northern townships along the Hudson River–Lake Champlain corridor (light blue triangles in figure 3).

To model NY, we first established the spatial origin of the epidemic. For CT, the disease clearly entered at one location and was first detected in Ridgefield Township in the southwest corner of the state. Unlike the epidemic in CT, the wave front of the epidemic reaching NY was irregular, and the disease entered at, and simultaneously affected, multiple locations. The first appearances of rabies in NY were clustered around four different locations (figure 1, green townships). Of interest, the point of introduction into CT at Ridgefield Township corresponds to one of the locations (figure 1, point d) where rabies may have entered NY along the Hudson River Valley and may indicate a focus of rabies established by long-distance translocation of infected raccoons, as adjacent portions of southeastern NY were affected at later dates.

Comparisons between CT and NY provided unique opportunities to explore how environmental heterogeneities influence rabies spread, as data from most states are not readily available at the spatial scale of townships. No scaling adjustments to our model were required since the density of townships is quite similar across states (see figure 5 in electronic Appendix A, available on The Royal Society's Publications Web site). However, the 7.7-fold greater area of NY with its sevenfold greater number of townships provided a challenge to our ability to predict disease spread over larger spatial domains.

2. MATERIAL AND METHODS

To predict rabies invasion across NY, we used a spatial stochastic simulation model developed previously to account for patterns of spread across CT. As the rabies virus is transmitted directly from raccoon to raccoon, local spread is assumed to occur between adjacent townships. Adjacency for this model was defined as two townships sharing at least one common point along their borders. An infected township, i, infects its adjacent neighbour, j, at rate λ_{ij}. In addition to local spread among adjacent townships, long-distance movement of disease is incorporated into the model by assuming a low and constant rate of global infection, μ_j, for all uninfected townships regardless of spatial proximity to infected neighbours (Smith *et al.* 2002).

The basic algorithm we used to simulate the epidemic involved five steps. First, we computed the total rate of infection in the jth township, ρ_j, where $\rho_j = \mu_j X_j + \Sigma_i \lambda_{ij} X_j (1 - X_i)$, $X_j = 1$ if the jth township is uninfected, and $X_j = 0$ otherwise. Second, we computed the total rate of infection for all townships, $\Lambda = \Sigma_j \rho_j$. Third, we computed the waiting time before the township becomes infected; we assume waiting times are exponentially distributed with rate parameter Λ. Fourth, we established a set of townships along the southern border of NY in which the disease was first introduced into the state. These townships are 'forced', meaning that infection in these townships was not simulated: once the time-index of the simulation passed the time when rabies was observed, their status was changed from uninfected to infected. These forced townships establish the boundary conditions for the advancing wave of rabies as it moved into the state. Finally, the state of the infected township was updated, and the algorithm was iterated until all townships were infected.

The model was parameterized using a stochastic global-optimization procedure. For each set of parameters, the epidemic was simulated 5000 times to generate the expected time of first appearance, E_i, for each township. For each simulation, we searched the parameter space for parameters that minimized the χ^2-statistic, $Y = \Sigma_i (O_i - E_i)^2 / E_i$, where O_i denotes the observed time of first appearance. In our previous paper, we used the time to first appearance across CT townships to parameterize the stochastic simulator. For a more detailed description of the model structure and parameterization as well as a discussion of alternative models, see Smith *et al.* (2002).

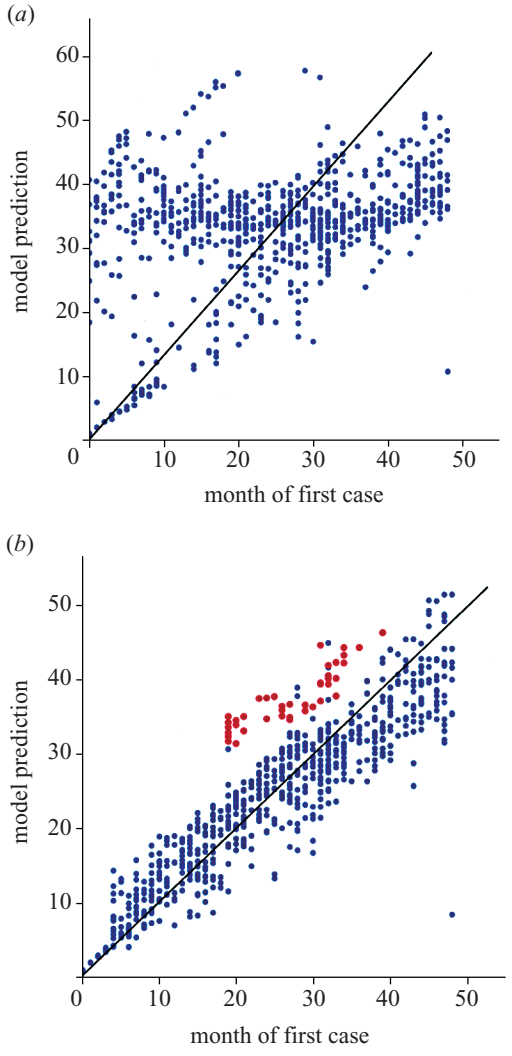

Figure 2. Relationship between the predicted time to first appearance (by township) and the observed time to first appearance (by township) using either single or multiple entry points for epidemic emergence in NY. (*a*) Single-entry model with best fit constrained through the origin ($y = 1.121x$, $R^2 = 0$, $p =$ n.s.). (*b*) Multiple-entry model with best fit constrained through the origin ($y = 0.952x$, $R^2 = 0.7974$, $p < 0.0001$). Points in red correspond to townships in the Hudson River–Lake Champlain corridor. Single-entry simulations fail to capture the observed dynamics of spread. Multiple-entry simulation accounts for *ca*. 80% of the observed pattern of spread.

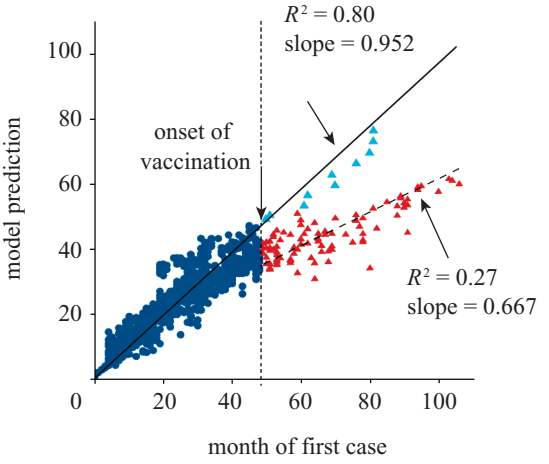

Figure 3. Relationship between model predictions and observed time to first appearance for the first 106 months of the NY epidemic. The best-fit line for the first 48 months is shown in solid black ($y = 0.9521x$, $R^2 = 0.7974$, $p < 0.0001$). The best-fit line after the onset of vaccination (red triangles) is shown by the dashed line ($y = 0.667x$, $R^2 = 0.27$, $p < 0.001$). The light-blue triangles correspond to townships in the northern portion of New York State along the Hudson River–Lake Champlain corridor (see figure 1). After vaccination townships experience a 30% reduction in rate of spread relative to that predicted by the general model.

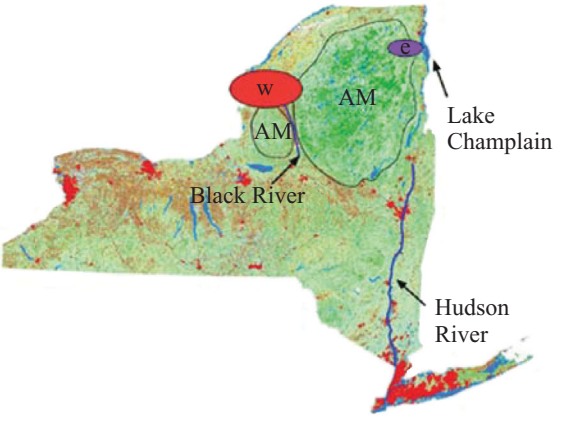

Figure 4. Vegetation map for New York State with major lakes and rivers indicated (NYS Gap Analysis, http://www.dnr.cornell.edu/gap/figure2_5.jpg). The AM are outlined in black. The dark-green colour seen in the AM represents coniferous forest. The two filled ovals, w and e, represent the relative magnitude and spatial location of the two primary 1995 vaccination strategies initiated to halt the northward expansion of rabies.

To evaluate the consequence of single versus multiple points of entry, we compared two simulations using different initial conditions for points of entry. The first assumed a single point of entry into NY corresponding to homogeneous regular wave dynamics from the point of the initial epidemic spread in West Virginia. The second model assumed four points of wave-front entry as suggested by the data showing near-simultaneous dates (January–March 1991) of first detection of raccoon rabies at those locations (figure 1).

We simulated the spread of rabies across NY using the previously derived best-fit parameters for CT ($\lambda_{ij} = 0.4676$, $\mu_j = 0.000\,294\,4$) and tested the two forcing functions corresponding to the two different initial conditions for entry of the NY epidemic. The first forcing condition used 60 townships clustered into the western corner of NY closest to the epidemic focus in West Virginia and would correspond to homogeneous and unimpeded flow from the initial focus of the epidemic on the West Virginia–Virginia border. These 60 townships comprise 8% of the state's infected townships. The second forcing consisted of forcing the four observed points of entry into NY State along the southern border. The 65 townships used for the second forcing function along the southern border comprise 8.6% of NY infected townships. This function more closely emulates the forcing function used in CT where all townships on the western border of the state were forced (*ca*. 6.6% of the 169 townships in that state).

3. RESULTS

For NY, for a single point of entry the model failed to capture the movement of the wave front (figure 2*a*; $y = 1.12x$, $R^2 = 0$, d.f. = 753, n.s.). However, when the epidemic was simulated using the same parameters and four points of entry, the model accurately predicts disease spread across the state (figure 2*b*; $y = 0.95x$, $R^2 = 0.80$, d.f. = 753, $p < 0.0001$). The fit of the model to the data was incrementally improved with each additional point of entry (from one to four) by emulating more closely the observed initial condition of the advancing wave front (data not shown). A film comparing observed data with model predictions based on multiple points of entry can be found in electronic Appendix B.

Though the simulations with multiple points of entry accurately predicted a majority of the cases during the first 48 months of the epidemic, a small cluster of townships reported rabies cases far in advance of model predictions (figure 2*b*, red points). These townships clustered along the Hudson River–Lake Champlain corridor.

The above results were drawn from simulations over the first 48 months of the epidemic. Using the same simulation parameters, we tested the predictive capabilities of the model over the first 106 months (including the first 48 months) corresponding to all the months where northward geographical expansion was observed. The model captured the dynamics of the first 48 months but we witnessed a significant deviation from the predicted rate of spread after month 48 (figure 3).

The predictions for the first 48 months of the 106 month simulation are identical to those of the initial model. After month 48, the plot of model predictions for the northeastern portion of the epidemic (figure 3, light-blue triangles, $y = 0.9521x$) remain on a similar trajectory to those of the first 48 months. However, large deviations from the model predictions are found for townships in the northwestern portion of the state ($y = 0.667x$, $R^2 = 0.27$, $p < 0.001$; figure 3, red triangles). Month 49 corresponds to the onset of a state-sponsored wildlife rabies-vaccination campaign in the townships surrounding the Adirondack Mountains (AM). Our simulations show a reduction in the rate of spread of *ca*. 30% at this juncture, indicating a possible consequence of raccoon vaccination.

4. DISCUSSION

Predicting disease spread with this model relied on knowledge of when and where the epidemic front reached NY. A single-entry-point model failed to capture the spread of disease (figure 2*a*). Environmental features between West Virginia and NY that impeded or promoted the rate of rabies wave-front advancement were described in Pennsylvania (Moore 1999). Geographical and demographic features are known to influence the rate and direction of disease spread in rabies (Moore 1999; Lucey *et al.* 2002) and variation in the arrival time and structure of the advancing wave front might also be influenced by long-distance translocation of rabid animals (Wilson *et al.* 1997; Smith *et al.* 2002). Long-distance translocation of raccoons has been associated with activities such as removal of household refuse, where truck drivers have observed raccoons spilling out during dumping (Wilson *et al.* 1997). Long-distance translocation would lead to isolated points of introduction far in advance of the progressing wave, which could initiate independent epidemics. In our data, three of the initial points of entry into NY (a, b and c; figure 1) were most probably the result of the influence of intervening geographical barriers while one point of entry (d) appears most probably to be the result of a long-distance translocation event corresponding to the initial epidemic expansion into CT.

Rivers in CT slowed the spread of rabies but rivers in NY exerted the opposite effect. Overall, townships along the Hudson River experienced raccoon rabies earlier than predicted by our model (figure 2*b*, red points). Riparian areas provide an excellent habitat for raccoons and corridors for rapid rabies spread. Superficially, this result appears to conflict with results from CT where a river separating two townships slowed rabies spread sevenfold. However, in NY the major trajectory of the advancing rabies wave front was parallel to the Hudson River, whereas in CT it was orthogonal to the major river systems. Hence, our models indicate how the directionality of the advancing rabies wave front relative to environmentally heterogeneous features dictates their effect as impediments or promoters of rate of spread.

The orientation of a river relative to the direction of epidemic expansion may not only slow the advance but also redirect the pattern of movement. In CT, the wave front was deflected north relative to its original easterly course as it met the Connecticut River barrier. Rivers may also accelerate the rate of rabies spread along corridors of prime raccoon habitat as appears to have occurred in NY.

Our analysis uses the CT model to predict the pattern in NY. How well would the model predict the CT pattern if we parameterized it using the NY data? Parameterization of the model against NY data generates extremely similar values to those for the CT data for both local and global rates of transmission ($\lambda_{ij} = 0.465$, $\mu = 0.0003$) without differentiating townships separated by rivers. This parameter set predicts the spatio-temporal pattern in CT as well as does the original parameter set when heterogeneity in local transmission caused by rivers is ignored.

The change in rate of spread after month 48 is coincident with the onset of mass vaccination of raccoons through state oral-vaccine delivery programmes (C. Trimarchi, personal communication; Hanlon & Rupprecht 1998) and a change in habitat and geographical features. In 1995, the New York State Department of Health and Cornell University began distributing oral vaccine for epizootic rabies control in the northern areas of the state (C. Trimarchi, personal communication). Vaccine delivery was targeted at two primary sites at the eastern and western edges of the AM range (areas 'w' and 'e' in figure 4). The vaccination programme was coordinated along the advancing front of the epidemic in the hope of halting further spread. Our results suggest that the vaccination programme may have effectively altered the population dynamics of the raccoon–virus interaction. Before the onset of vaccination, spread follows the pattern predicted by the CT model. However, after vaccination, the average rate of spread is markedly reduced relative to the rate predicted by the model (*ca*. 30% reduction in slope after month 48; figure 3).

This conclusion may be confounded, however, by the simultaneous effect of the wave front reaching the AM region. The AMs correspond to a significant change in habitat and forest composition (from deciduous forest to coniferous forest) and this change would have a substantial effect on raccoon population densities and movement. Coniferous forests are not a preferred habitat for raccoons, and their density in these habitats is extremely low (Godin 1977).

The data may reflect the changes in habitat, the impact of vaccine delivery on rates of local propagation after month 48, or most probably an interaction between these two factors. The rate of spread in townships on the western boundary of the AM is slower than that on the eastern boundary, and spread in both regions is slower than that in the southern region prior to month 48. The rapid spread in the east (light-blue triangles, figure 3) may reflect the combined effects of the high rate of spread along the Hudson River–Lake Champlain corridor and the increased distance between the location of initial vaccine delivery and the location of the advancing epidemic wave front. Future work will focus on disentangling and quantifying the relative impacts of vaccination and habitat change.

The strength of our analysis is twofold. First, we have been able to show that predictive *a priori* models of disease spread can be built and applied to the expansion of disease into novel geographical regions. While some models have been developed to account for the *ex post facto* pattern of spread, this may be the first demonstration of *a priori* model prediction over spatial domains. This model framework is equally suitable for predicting the initial epidemic front of other wildlife diseases that are spread primarily through a local contact process, i.e. tuberculosis in badgers.

Our model does not explicitly incorporate traditional forms of density dependence within racoon populations or on the transmission process. Yet, our models can, fairly accurately, account for patterns of spread. The ability to make predictions without incorporating density-dependent regulatory mechanisms may be a consequence of our focus on the advancing front of the epidemic wave where population processes are anticipated to be largely controlled by density-independent factors (Shigesada & Kawasaki 1997).

Second, after validating the model's predictive value over a given region, we can use deviations from model predictions as a means of identifying and assessing the effects of new environmental heterogeneities on patterns of spread. In our case, model projections revealed distinct clusters with reduced rates of spread, suggesting a potential partitioning of environmental effects. Vaccination may have slowed the advancing wave front but simultaneously the slowing effect may have been negated by the increased rate of spread along the Hudson River–Lake Champlain corridor. Such partitioning of effects revealed by model projections should be useful in assessing the efficacy of disease-management and vaccination strategies across heterogeneous landscapes.

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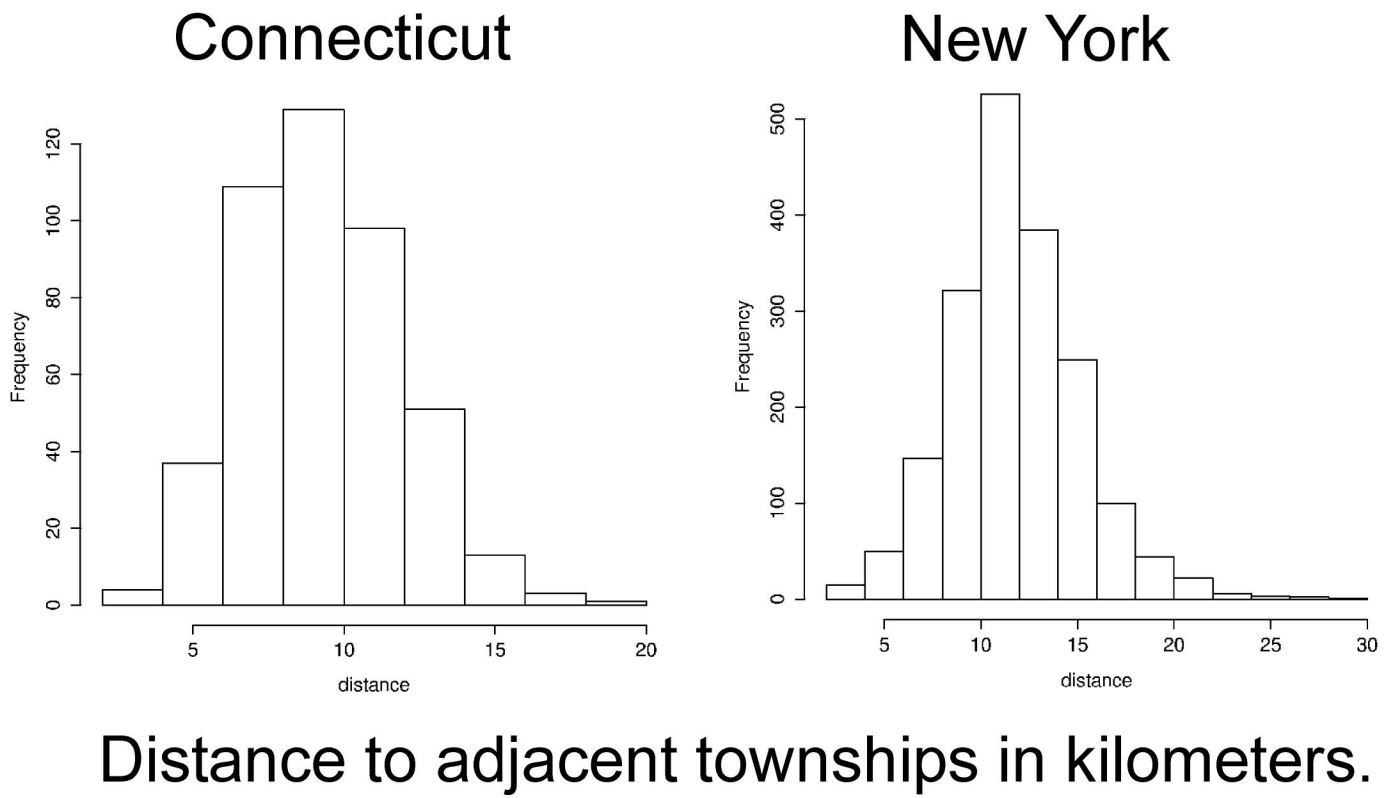
This is an electronic appendix to the paper by Russell *et al*. 2003 *A priori* prediction of disease invasion dynamics in a novel environment. *Proc. R. Soc. Lond.* B **271**, 21–25. (DOI 10.1098/rspb.2003.2559.)
Electronic appendices are refereed with the text. However, no attempt is made to impose a uniform editorial style on the electronic appendices.

Electronic appendix A. Figure 5. Distribution of distances between adjacent neighbours in Connecticut and New York.



Electronic appendix B
The movie shows the invasion of raccoon rabies in New York State from January 1991 to January 1995. The frame on the left shows the observed data from the New York Department of Health. The frame on the right shows the model predictions. The movie plots a frame every two months.