Research Paper

Spatiotemporal Analysis of Epizootic Raccoon Rabies Propagation in Connecticut, 1991–1995

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ABSTRACT

The quantitative analysis of pathogen transmission within its specific spatial context should improve our ability to predict and control the epizootic spread of that disease. We compared two methods for calibrating the effect of local, spatially distributed environmental heterogeneities on disease spread. Using the time-of-first-appearance of raccoon rabies across the 169 townships in Connecticut, we estimated local spatial variation in township-to-township transmission rate using Trend Surface Analysis (TSA) and then compared these estimates with those based on an earlier probabilistic simulation using the same data. Both the probabilistic simulation and the TSA reveal significant reduction in transmission when local spatial domains are separated by rivers. The probabilistic simulation suggested that township-to-township transmission was reduced sevenfold for townships separated by a river. The global effect of this sevenfold reduction is to increase the time-to-first-appearance in the eastern townships of Connecticut by ~29.7% (spread was from west to east). TSA revealed a similar effect of rivers with an overall reduction in rate of local propagation due to rivers of ~22%. The 7.7% difference in these two estimates reveals slightly different aspects of the spatial dynamics of this epizootic. Together, these two methods can be used to construct an overall picture of the combined effects of local spatial variation in township-to-township transmission on patterns of local rate of propagation at scales larger than the immediate nearest neighboring townships. Key Words: Trend Surface Analysis—Local habitat variation—Rabies—Raccoon-Disease spread. Vector Borne Zoonotic Dis. 2, xxx–xxx.

INTRODUCTION

THE TRANSMISSION OF A PATHOGEN among hosts is inherently a spatially dependent process. Geographic variation in local environmental variables plays a major role in limiting host and pathogen population densities, and thus affects the number of potential interactions between a pathogen and its host. These spatially dependent interactions can, in turn, alter the velocity and direction of infectious disease propagation. Presently, most models of disease dynamics assume populations are homogeneously mixed and not spatially structured (Holmes 1997). Indeed, much of modern epidemiological theory discounts the effects of

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space on pathogen transmission. The quantitative analysis of disease within its specific spatial context will undoubtedly improve our ability to predict and control the spread of that disease (Bolker et al. 1995, Real and McElhany 1996, Dobson 2000, Smith et al. 2002). In this paper, we illustrate one method for calibrating the effect of local, spatially distributed environmental heterogeneities on disease spread and compare the rate estimates with those obtained from a probabilistic simulation previously reported by Smith et al. (2002).

Rabies provides an excellent system for exploring the relationship between local environmental variables and the spatial and temporal structure of an advancing disease front. Rabies virus transmission requires direct contact between a rabid and a susceptible animal. Since the mid-1970s an advancing epizootic of raccoon rabies has swept the eastern seaboard of the United States (Childs et al. 2000, Smith et al. 2002). The origin of this epizootic appears to have been associated with the transport of rabid raccoons from Florida to the West Virginia/Virginia border, where they were released for sport hunting (Nettles et al. 1979).

Locally, the wave front shows considerable variation in rate of propagation. Some of this local variation in velocity has been attributed to the effects of local habitat variation. In their statistical analysis of the pattern of rabies spread across Pennsylvania, Moore (1999) and Moore and Carpenter (1999) suggested that the Allegheny Mountains affected the velocity and direction of movement of rabies across the state. However, no quantitative analysis was undertaken to establish this relationship. Using data from Connecticut, Wilson et al. (1997) examined the spatiotemporal pattern of disease occurrence at different phases of that state's epizootic, and the pattern clearly shows non-homogeneous spread over time. Until only recently, however, there have been no spatiotemporal mathematical models for predicting raccoon rabies spread across heterogeneous landscapes.

In an earlier paper (Smith et al. 2002), we developed a general method for quantifying spatial variation in rates of disease spread across heterogeneous spatial landscapes, and developed a stochastic spatial model for the spread of rabies across Connecticut's 169 townships. We created an interaction network among townships where the local rate of spread into uninfected townships was a function of the fraction of adjacent townships that were already infected. Local rates of spread also were potentially a function of key topographic and human demographic characteristics of the townships, namely, their proximity to a river boundary, local human population density, and the likelihood of long-distance transport of infected raccoons. We found that large rivers act as semipermeable barriers to local transmission leading to a sevenfold reduction in the local rates of propagation across neighboring townships.

In this report, we used a modified form of analysis first suggested by Ball (1985) for assessing the relationship between local environmental conditions in France and the pattern of spread of fox rabies in Europe. The overall approach involves a three-step procedure. Data are assembled indicating the local time of first appearance of the disease at different geographic locations. This constitutes the raw time structure of the detected front of a disease epizootic. Second, the raw data are statistically analyzed for variation in the rate of local disease propagation. Third, quantitative assessments of local transmission rates are correlated statistically with quantitative measures of local topographic and demographic features. In this way, we directly determined the statistical magnitude of the contribution of different environmental variables to the rate of local transmission.

This technique is an alternative to the stochastic simulator techniques of Smith et al. (2002). Our previous analyses focused on a method for assessing the quantitative variation in transmission rates across neighboring townships. In this report, we use Ball's (1985) method to ascertain the rate of rabies propagation at a spatial scale that incorporates the interaction of several neighboring townships. We illustrate how the combination of the two methods leads to a greater ability to understand the relationships among transmission rates at differing spatial scales.

MATERIALS AND METHODS

The study system

Rabies in domestic and wild animals has been a nationally notifiable disease, reportable to the Centers for Disease Control and Prevention since 1961. Data are most often collected at the unit of the individual county. However, for a few states data are available at a higher resolution. The State of Connecticut has compiled data from each of the 169 townships that make up its eight counties, providing a >20-fold increase in spatial resolution over other similar surveillance data.

Raccoons throughout Connecticut that were sent to government laboratories were tested for rabies infection by standard direct fluorescent antibody methods (Trimarchi and Debbie 1991) at either the Bureau of Laboratories, Connecticut Department of Public Health (Hartford) or the Departments of Pathobiology, University of Connecticut (Storrs) and the location by township of all tested animals ascertained. This analysis includes all positive raccoons recorded from the initial introduction in March 1991 through April 1995.

Time to first appearance

Raccoon rabies entered Connecticut from the southwest at Ridgefield Township in March 1991, progressing eastward across the state until reaching the easternmost townships by the end of 1995. There were 2,643 total cases of raccoon rabies reported from the 169 townships of Connecticut over the 49-month period of the initial epizootic spread. All townships were assigned a date of first appearance of rabies relative to the epizootic's start date in Ridgefield Township (Fig. 1).

Trend Surface Analysis (TSA)

Local variation in transmission rates were assessed at an aggregated spatial scale, rather

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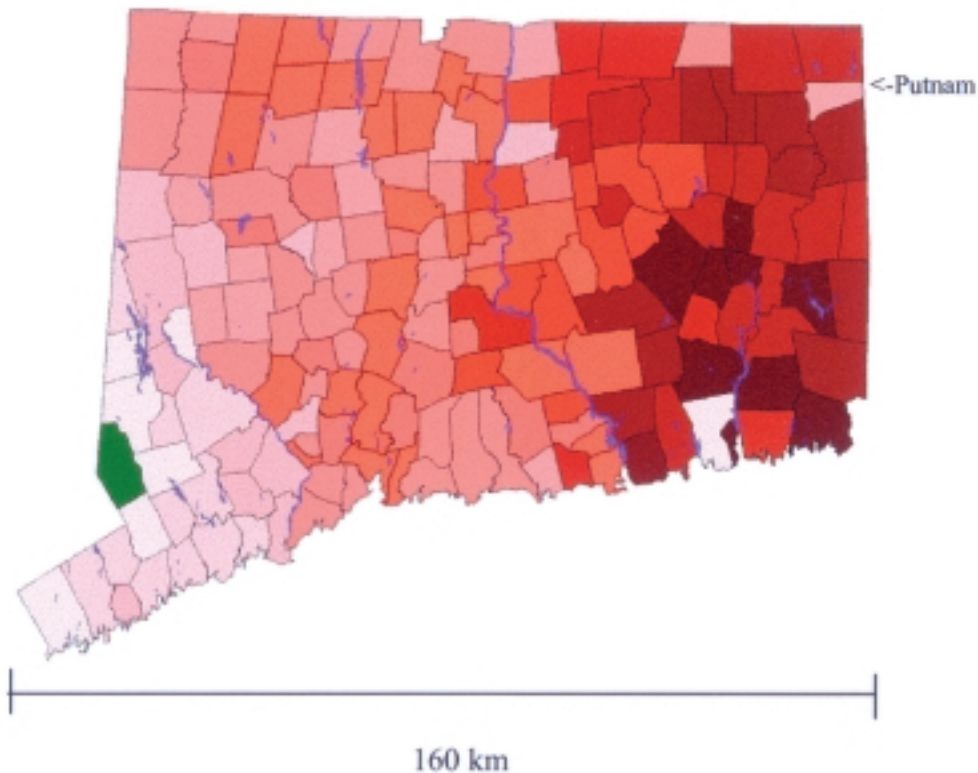
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FIG. 1.   The month when rabies was first observed in each township, relative to the month of the first reported case in Ridgefield Township (in green), in March 1991 in western Connecticut. The color of each township indicates the number of months that elapsed from the time that rabies was first reported, with darker red indicating later times.

than at the level of adjacent townships, by using TSA, a global surface fitting procedure that uses a multidimensional polynomial to construct a smoothed surface from the data by least-squares estimation (Krumbein and Gaybill 1965, Cressie 1993). TSA has previously been used to identify possible disease corridors in other studies of rabies (Moore 1999, Moore and Carpenter 1999).

Using TSA, a deterministic linear model was developed to relate the movement of the epidemic wave front to underlying physical and biological factors, inherent in geographical locations across Connecticut. This model allows multivariate data to be expressed in a nonlinear manner but still enables least-squares methods to be applied to find the most suitable model. More specifically, using least-squares linear model techniques, a polynomial surface is fitted to the set of spatially distributed times of first appearance of rabies across the 169 townships. For township i, the time of the first report of a rabid raccoon is denoted $T_i(X_i,Y_i)$ where X_i and Y_i are the east–west and north–south coordinates, respectively, for that township. The general model for a given location is decomposed into a trend component and an error component and is given by $T_i(X_i,Y_i) = t(x_i,Y_i) + \epsilon_i$, where $t(x_i,Y_i)$ is the trend and ϵ_i is the associated error term at the ith location. A generalized polynomial model is used to describe the relationship among X, Y, and the trend $t(X,Y)$. The general trend is assumed to be described by $t(X,Y) = \sum_{p=0}^{N} \sum_{q=0}^{N} d_{pq}X^pY^q$, where N corresponds to the order of the polynomial model and the polynomial coefficients, d_{pq}, are chosen through the use of least-squares regression to minimize the deviation of the resulting surface from the observed data.

The shape and flexibility of the trend surface are determined by the order of the polynomial chosen as the model. A first-order polynomial restricts the trend to a plane through the data. Second-order polynomial models allow for curvature over the entire data set. Higher-order models allow for much more local curvature in the fitted surface. Standard techniques can be used to statistically evaluate the improvement in the model's fit as one moves from lower- to higher-order polynomials. We estimated the best trend surface using first-order through fourth-order polynomial models (i.e., linear through quartic surfaces) using S-Plus 2000 (MathSoft, 1999). Model selection was based on a version of Akaike's Information Criterion (AIC) equivalent to Mallows' C_p criterion. This selection criterion penalizes the residual sum of squares by twice the number of parameters times the residual mean square for the initial model, and seeks to minimize this criterion at each step. Venables and Ripley (1994, p. 175) noted that this selection criterion is similar to conventional F tests, but with a smaller critical value leading to an approach that is cautious in removing and generous in adding variables. This is appropriate in our case, as our goal is a best-fit model providing local detail in the prediction surface, not necessarily the most parsimonious set of covariates providing adequate fit to the data.

Estimates of the local rate and direction of the spread of the disease were assessed as the directional derivative at each township's centroid using the best-fit surface for a given order of polynomial model. Along the fitted surface, direction is orthogonal to the level curves of the surface, and speed is the inverse of the slope along the direction of movement. The set of directional derivatives for each order surface were assembled into a vector field where the length and angular deviation of each arrow indicates the velocity and direction of disease propagation from each township centroid. We constructed four different vector fields corresponding to the four different order surfaces. The vector field provides a visual representation and quantitative assessment of the pattern of the direction and velocities of local spread over the entire geographic region.

Rivers and the rate of local disease spread in TSA

We suspected that rivers could be an obstacle to rabies transmission from our previous results (Smith et al. 2002), and thus scored townships according to their proximity to the three major waterways in Connecticut. Connecticut comprises three separate watersheds that drain into the Thames, Connecticut, and Housatonic Rivers. All other rivers in Connecticut are tributaries of these three rivers

(Patrick McGlamery, Map Librarian, University of Connecticut, personal communication; http://magic.lib.uconn.edu). We restricted our analysis to these major rivers since they will presumably have the largest effects on transmission dynamics.

As the wave front was moving in an easterly direction, rivers presented a major barrier to the movement of rabid raccoons outside of a township when a river covered the majority of that township's eastern border. For analytic purposes, a township was scored as 1 if a river covered 75% of the eastern border or 0 if a river covered <75% of the township. This demarcation principle was derived through the following logic. If a township was situated so that 100% of the township is to the west side of a bordering river, then there is no ambiguity in

assigning that township. If the river bisects a township so that 50% of the township is on the west and 50% on the east then, this township is maximally ambiguous. Thus, 75% cover corresponds to the midpoint between township assignments that are maximally and minimally ambiguous with respect to the river.

The interaction between local rates of disease propagation measured as the vector length of the directional derivative and proximity to a river boundary was assessed by analysis of variance.

RESULTS

TSA

All four of the best-fit trend surfaces for the time-to-first appearance showed an overall in-
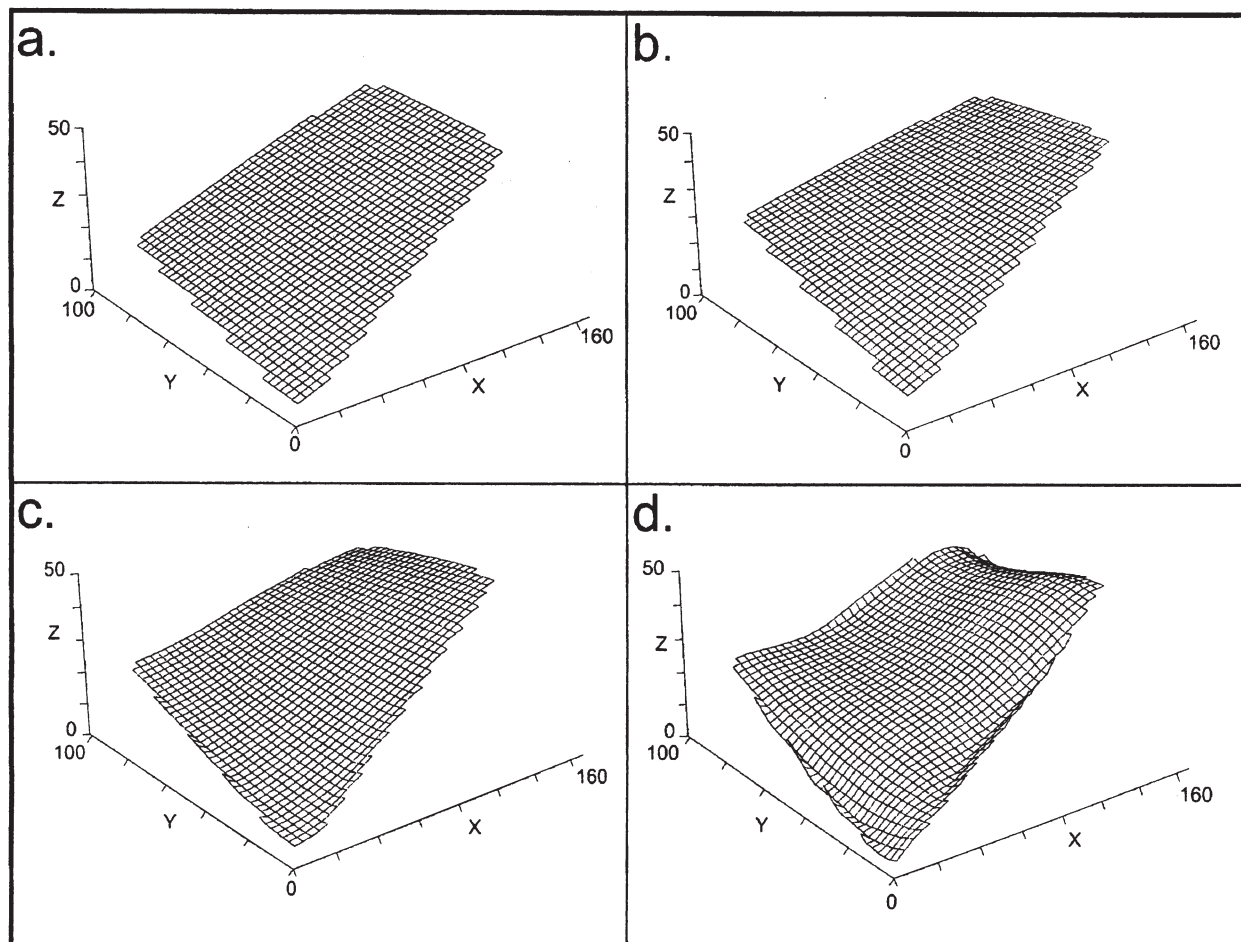
FIG. 2. Best-fit trend surfaces for the different order polynomial models used to fit the time to first appearance of raccoon rabies across the 169 townships in Connecticut: **(a)** first-order polynomial (linear model), **(b)** second-order polynomial (quadratic), **(c)** third-order polynomial (cubic), and **(d)** fourth-order polynomial (quartic). The (x,y) coordinates correspond to east–west and north–south directions in kilometers, respectively.

crease in slope toward the east (Fig. 2). The best-fit first-order polynomial trend surface (Fig. 2a) is given by $Z = 3.8 + 0.0118X + 0.0176Y$ ($R^2 = 0.76$, $df = 165$, $F = 268$, $p < 0.001$). The best-fit second-order polynomial (Fig. 2b) corresponds to $Z = -1.32 + 0.345X + 0.141Y - 0.002XY$ ($R^2 = 0.78$, $df = 164$, $F = 199.3$, $p < 0.001$). The third-order trend surface (Fig. 2c) is given by $Z = 4.31 + 0.093X + 0.003Y^2 + 0.002Y^2 + 0.0001X^3 + 0.0001XY^2$ ($R^2 = 0.79$, $df = 162$, $F = 125.4$, $p < 0.0001$). The best-fit fourth-order polynomial (Fig. 2d) is given by $Z = 1.59 + 0.92X - 0.72Y - 0.027X^2 + 0.01Y^2 + 0.0003X^3 + 0.00004X^4 + 0.025XY - 0.0004XY^2 + 0.00001YX^3 + 0.00001X^2Y^2 + 0.00001XY^3$ ($R^2 = 0.82$, $df = 155$, $F = 59.2$, $p < 0.0001$). Each model represents the result of a stepwise regression selection of the best-fitting model among models up to a certain polyno-

mial degree. While qualitatively the models provide similar fit (Fig. 2), we note the models are not nested (i.e., higher-order models involve more than simply adding higher-order terms to best-fit lower-order models), and statistical tests comparing full and reduced models do not directly apply. We focus attention on the best-fit quadratic model since it provides overall fit (in terms of R^2 and the overall F test) and predictions (Fig. 2) comparable to the best-fit lower-order models, while allowing the increased flexibility to capture local features in the data.

The data are dominated by the overall trend with a very strong and significant east–west component. A linear model precludes any possibility of detecting local variation. Successive order trend-surfaces capture successively finer local variations. The best-fit second-order sur-
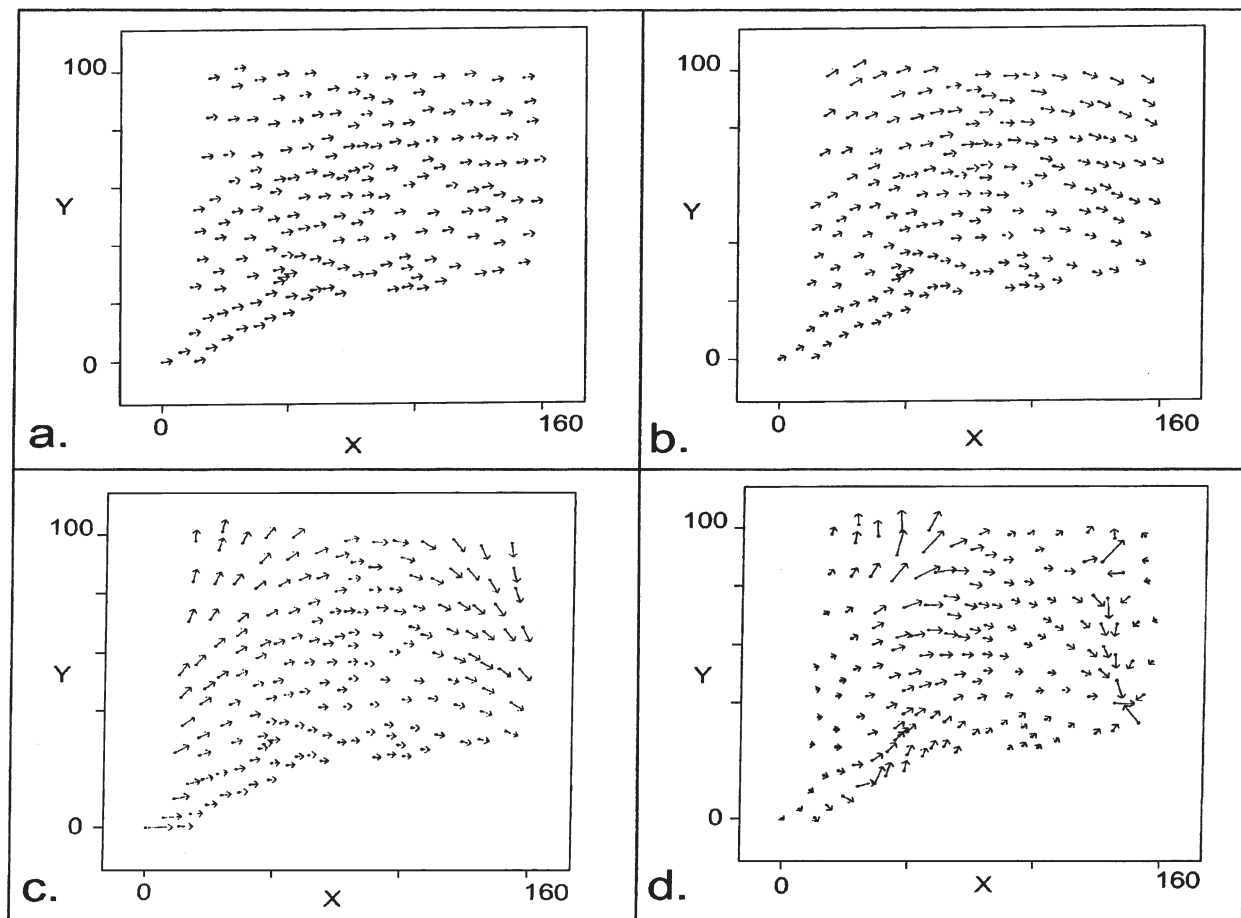

FIG. 3. **Vector field representation of the best-fit trend surface for each of the polynomial models for time to first appearance of raccoon rabies across Connecticut.** Each arrow is anchored at the township centroid and represents the local velocity and direction of disease propagation from that township centroid. Vector fields correspond to the (**a**) linear, (**b**) quadratic, (**c**) cubic, and (**d**) quartic polynomial best-fit trend surfaces.
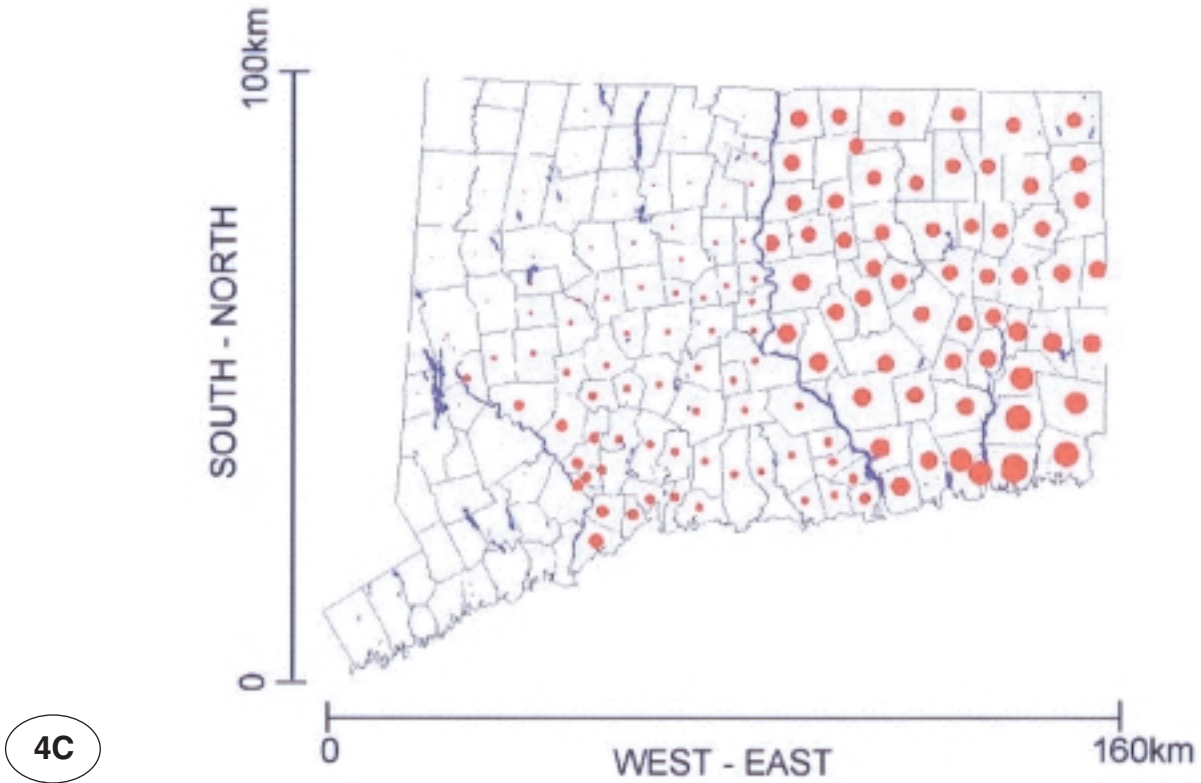
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FIG. 4. Comparison of the time to first appearance in the probabilistic simulations with and without rivers present within the simulations. The size of each red circle indicates the magnitude of the difference between the two simulations. By the time the epizootic reached the eastern portion of the state, the delay was ~14 months.

face allows some curvature of movement across the State and indicates a primary flow to the Northeast, East, and Southeast in the western, middle, and eastern thirds of the state, respectively. The best-fit third-order surface captures some slower movement of the disease in the Northeast. It is only with the best-fit fourth-order surface, however, that the fitted surface allows enough flexibility to reveal some local variation in the speed of propagation. The
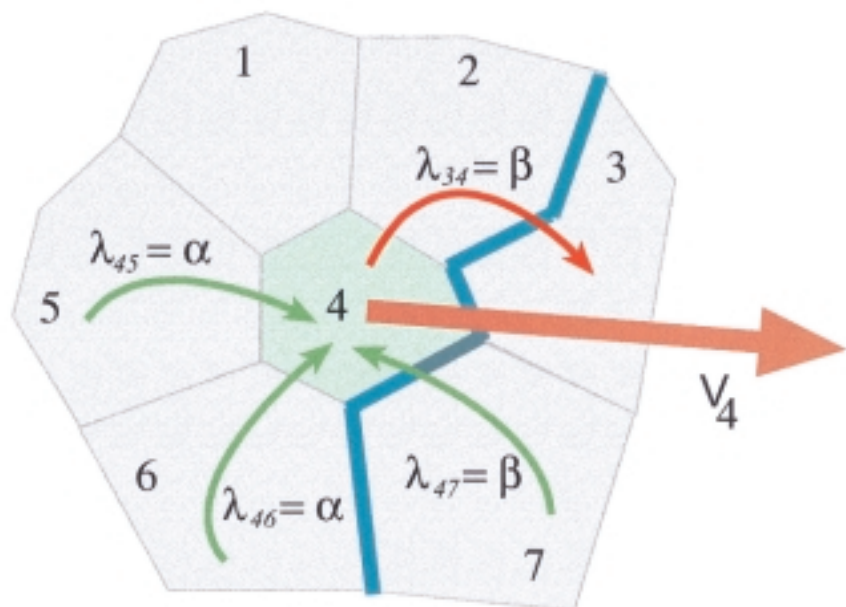
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FIG. 5. Diagrammatic representation of the combined effect of neighbor-neighbor transmission rates (λ_{ij}) on the overall average velocity of spread from a given township centroid (V_4). Green arrows indicate neighbor–neighbor transmission into a target township. The red arrow indicates transmission from a target township. Transmission into and out of a given township pair will depend upon whether the townships are separated by a river.

best-fit fourth-order trend surface was executed using stepwise regression using the AIC (equivalently Mallows' C_p criterion), and higher-order terms are significant (Venables and Ripley 1994, p. 175).

The steeper portions of the fourth-order surface correspond to the areas where the wave front traveled the slowest. There appears to be an increase in slope occurring at ~110 km from the western border. This reduction in velocity traversed the state from North to South, and corresponded to the location of the Connecticut River. Vector field representations of the local rates of propagation for all four trend surfaces (Fig. 3) indicate that the most rapid rate of spread seems to occur just prior to this center line of the state, which corresponds to the river.

Local velocity and the effect of major rivers

The rate of propagation of rabies from a given township was significantly affected by the presence or absence of any river along its eastern border. Townships with the Thames, Housatonic, or the Connecticut River on their eastern border had a mean vector length significantly reduced from a mean of 3.86 km/month to 3.04 km/month ($t = 1.955$, $df = 166$, $p = 0.026$). Consequently, the effect of townships separated by major rivers ascertained by TSA suggests that rivers effectively reduced the average rate of spread by ~22%.

DISCUSSION

The data on raccoon rabies cases in raccoons from Connecticut provide a unique opportunity to characterize the spatial dynamics of an ongoing epizootic. These data also allow for a comparison among alternative techniques for assessing the effects of spatial heterogeneity on patterns of local spread.

Wilson et al. (1997) estimated that the raccoon rabies wave front for Connecticut traveled at an average velocity of ~30 km/year. With the added data since their paper and with our detailed analysis of township patterns of first appearance, we conclude that the frontal wave of rabies propagation is occurring at ~46 km/year. Our estimate of the velocity of the wave front is consistent with those obtained by Moore (1999) in her analysis of rabies spread across Pennsylvania (38.2 km/year) and slightly less than Ball's (1985) estimate of fox rabies spread in Europe (61.9 km/year).

The local rate of disease propagation appeared to be significantly affected by local environmental heterogeneities. Rivers clearly play an important role in the propagation of rabies across the state of Connecticut. The results we obtained here can be used in conjunction with the results from our probabilistic simulation (Smith et al. 2002) to arrive at a general model for the effect of environmental heterogeneity on rates of disease propagation at different spatial scales.

In the probabilistic simulator the likelihood of a township changing from infected to uninfected was determined by the sum of the transmission rates from one township to another. We found a sevenfold reduction in township-to-township transmission when townships were separated by a river. However, the probabilistic spatial simulation was based on an interaction network of the adjacent townships. Spatial heterogeneity was incorporated into this interactive network model by allowing the local rates of transmission across adjacent townships (λ_{ij}) to vary among the townships depending on their human demographic or geographic features.

A comparison of simulations, first with rivers present and then with rivers removed using the best maximum likelihood estimates for each λ_{ij} within the probabilistic simulation, suggested that the presence of rivers slowed the spread of rabies across Connecticut by ~12–14 months (Fig. 4). In the absence of rivers, rabies should have crossed the state in 37 months, while the fact that rivers were present slowed statewide propagation to ~48 months. The overall local velocity of the epizootic can be viewed as the product of all pairwise transmission events across townships. The probabilistic model suggests that the *overall* global effect on temporal delay due to the sevenfold reduction in transmission across river-separated townships generated a 29.7% reduction in the average rate of spread. This reduction is ~7.7% greater than the reduction in local velocity using TSA.

There are few data from field observations of raccoon rabies transmission across rivers with which to compare our analysis. That rivers only partially restrict spread of rabies among raccoons was demonstrated when infection was identified among raccoons in Ontario, Canada (Wandeler and Salsberg 1999), which is separated by the St. Lawrence River from northern New York, where raccoon rabies had been epizootic during 1998–1999 (Rosatte et al. 2001). The distance across the St. Lawrence River at this site was ~1 km, yet ear-tagged raccoons have been shown to cross the river at this location (Rosatte et al. 2001). At another river border along the Niagara River, however, introduction of raccoon rabies into Canada from an enzootic focus in the United States has not yet been detected, although raccoons also cross the river at this location (Rosatte et al. 2001). The potential that accidental translocations of rabid raccoons may breech these natural restrictions may be considerable, as shown by vehicular transport of infected raccoons into locations previously free of disease (Wilson et al. 1997, Rosatte et al. 2001). In addition, in Europe where red fox rabies is enzootic, rivers are considered to be natural barriers to rabies spread, with transmission occuring primarily where bridges are available (Wandeler et al. 1988).

The two methods of analysis we used—TSA and Probability Modeling—suggest the following overall picture of rabies spatial dynamics (Fig. 5). A target township (No. 4 in Fig. 5) is experiencing a combination of neighbor–neighbor transmission events (λ_{ij}), which sometimes is driven by α and sometimes by β depending upon whether the townships are separated by a river. The net resolution of these individual transmission events produces an averaged local rate of propagation (V_4), which is roughly revealed by the vector field corresponding to the Trend Surface. This Trend Surface vector field seems to generate differentials between river and non-river townships that are slightly lower than the probabilistic model. This differential may be due to the TSA smoothing over larger areas of the spatial data set, which ignores smaller-scale spatial variation.

While assessing the global structure of epizootics is important, local management strategies will often be tied to smaller-scale conditions. Knowledge of transmission dynamics at a fine spatial scale, which is affected by small-scale variations in local habitat, may allow better targeting of areas for surveillance and wildlife control. The methods and approach we describe here should prove equally applicable to other disease systems that are subject to local variation in habitat. These quantitative techniques for linking habitat variation and local transmission dynamics bring us one step closer to developing a synthetic predictive theory of infectious disease dynamics.

ACKNOWLEDGMENTS

ABBREVIATIONS

AIC, Akaike's Information Criterion; TSA, Trend Surface Analysis.

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