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Spatial Dynamics and Molecular Ecology of North American Rabies

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Abstract

Rabies, caused by a single-stranded RNA virus, is arguably the most important viral zoonotic disease worldwide. Although endemic throughout many regions for millennia, rabies is also undergoing epidemic expansion, often quite rapid, among wildlife populations across regions of Europe and North America. A current rabies epizootic in North America is largely attributable to the accidental introduction of a particularly well-adapted virus variant into a naïve raccoon population along the Virginia/West Virginia border in the mid-1970s. We have used the extant database on the spatial and temporal occurrence of rabid raccoons across the eastern United States to construct predictive models of disease spread and have tied patterns of emergence to local environmental variables, genetic heterogeneity, and host specificity. Rabies will continue to be a remarkable model system for exploring basic issues in the temporal and spatial dynamics of expanding infectious diseases and examining ties between disease population ecology and evolutionary genetics at both micro- and macro-evolutionary time scales.

Introduction

Rabies virus is a negative-sense, single-stranded RNA virus belonging to the genus *Lyssavirus* (Rhabdoviridae). With a cosmopolitan distribution and diverse mammalian reservoir of domestic dogs, wild terrestrial carnivores, and bats, rabies is a significant worldwide public health problem and is arguably the most important viral zoonotic disease. Annually, some 30,000–50,000 human deaths in developing nations are attributed to rabies; and within developed nations, management and prevention activities are costly. In 1997, approximately $300,000,000 was spent on rabies control in the United States, and as many as 45,000 U.S. residents received postexposure prophylaxis (PEP) (Krebs et al. 1998). Due to ongoing epizootics of wildlife rabies in Europe and North America, rabies remains a threat, even where domestic dog–transmitted rabies, the primary global concern, has been controlled.

Rabies has also proven to be a remarkably valuable system for exploring ecological and evolutionary processes in host–pathogen interactions. In Europe and North America, outbreaks of rabies have been chronicled in detail since the 1940s. In Europe, Canada, and Alaska (with incursions into New England), the major epizootic has been associated with red foxes (*Vulpes vulpes*) and their distinctive rabies virus variant. In contrast, outbreaks of rabies in the United States have involved multiple hosts and several different rabies virus variants, each primarily associated with a single mammalian species that serves as the reservoir. The ability to partition animal rabies into discrete compartments of a single distinct virus variant and a reservoir host species has been a defining achievement in our understanding of rabies epidemiology and has only recently been achieved through the application of monoclonal antibodies and genetic sequencing (Rupprecht et al. 1987; Smith et al. 1992; Smith and Seidel 1993; Smith et al. 1990). Human exposure to rabies virus is ultimately linked to transmission cycles in animals, and wildlife make the greatest contribution to annual total rabies cases in the United States (Krebs et al. 2001). It is probable that human rabies exposure in the United States has approached a level that cannot be further reduced without targeting wildlife for rabies control.

Once established within a particular animal population, rabies virus transmission can persist for decades, perhaps for centuries. Rabies has been endemic in Arctic fox (*Alopex lagopus*) and red fox (*V. vulpes*) populations of Alaska and Canada (Tabel et al. 1974) and in raccoon (*Procyon lotor*) populations of the southeastern United States for at least

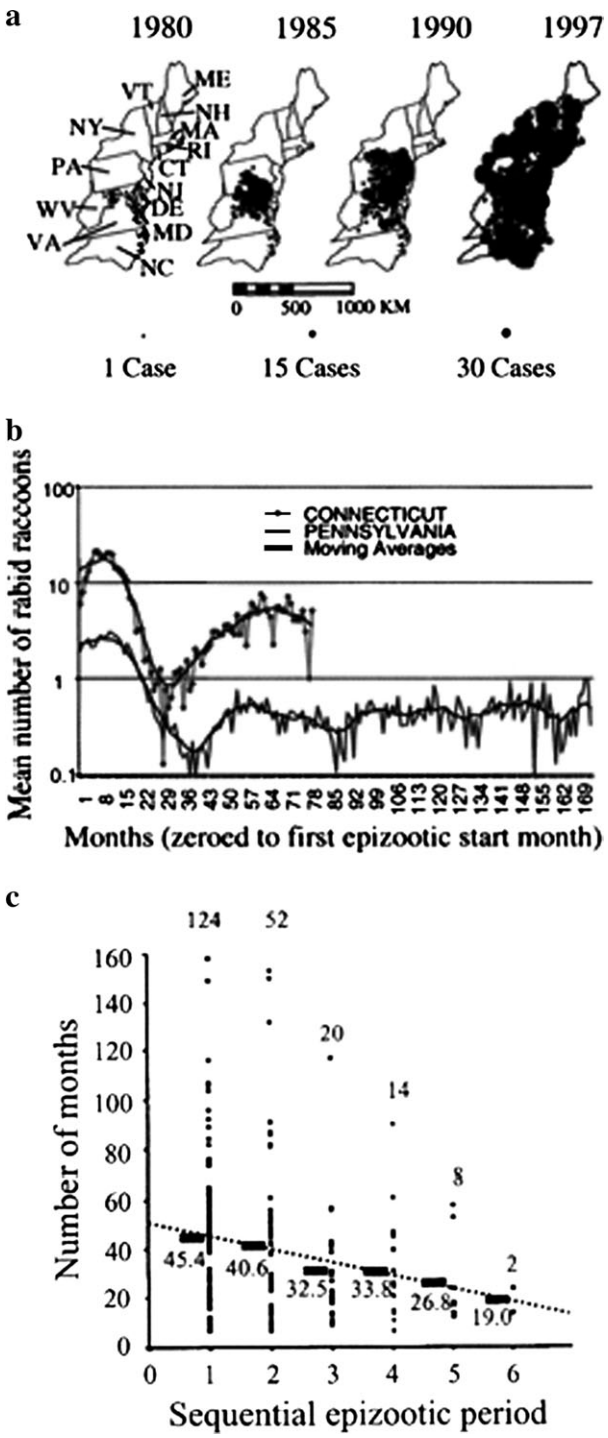

Figure 1. The spread of epizootic rabies among raccoons in the mid-Atlantic and northeastern United States from a focus on the Virginia/West Virginia border illustrated in selected years from 1980 through 1997. (a) The size of the dot is proportional to the annual totals for reported rabid raccoons centered by individual counties within a state. (b) Examples of the time series of mean monthly reports of rabid raccoons from counties within Pennsylvania and Connecticut. The black line represents 11-month moving averages of the monthly counts of rabid raccoons. (c) Statistical estimate of successive epizootic periods from time series data across states by county showing a significant decline in average epizootic period as the epizootic progresses within a given county. The average period declined by 4.82 months across successive epizootics. The average period of the first epizootic is approximately 45 months, which is remarkably consistent with the period predicted by the dynamical systems model for raccoon rabies developed by Coyne et al. (1989) (after Childs et al. 2000).

50 years (Burridge et al. 1986). Annual fluctuations in the numbers of rabid animals reported from specific locales are the rule; but frequently, the disease persists at low levels (endemic or enzootic).

The rabies virus can cause sensational epizootics. The epizootic associated with raccoons in the eastern United States is believed to have been initiated in the mid-Atlantic region by the interstate translocation of raccoons incubating rabies from an established focus of raccoon rabies in the southeastern United States for the purpose of restocking dwindling local populations (Nettles et al. 1979; Smith et al. 1984). Since the mid-1970s, this raccoon-adapted variant of the rabies virus has spread north to Maine and Ontario, Canada, and west to Ohio, causing one of the most intensive outbreaks of animal rabies ever recorded (Figure 1a). The magnitude of this epizootic was enhanced by the spread of the virus through naive raccoon populations of very high density, often in states that had not experienced terrestrial rabies for decades (Rupprecht and Smith 1994). Coincident with epizootic spread has been an increased requirement for postexposure treatment in humans. For example, in New York state, the number of individuals receiving postexposure prophylaxis increased from 84 in 1989, prior to the introduction of raccoon rabies, to 1,125 in 1992 and 2,905 in 1993 (Anonymous 1994; CDC 1997).

Temporal Dynamics in Raccoon Rabies in the Eastern United States

The lethal consequence of rabies infection for most mammalian hosts has led to particularly well-defined waves of epizootic spread. The spatial dynamics of epizootic rabies in red foxes has been modeled in Europe by several investigators (Bogel et al. 1976; Murray and Seward 1992; Murray et al. 1986; Steck and Wandeler 1980). However, the development of models for raccoon rabies population dynamics and wave spread in the United States has only been recent.

Coyne et al. (1989) constructed an a priori model of rabies population dynamics to predict the change in the total raccoon population size—partitioned in categories of susceptible raccoon hosts (X), exposed hosts (i.e., H_1, infected but not infectious), hosts exposed that develop immunity (H_2), rabid hosts (Y), and hosts that are immune (I)—using the following set of differential equations:

$$
\begin{aligned}
dX/dt &= a(X+I) - (b+\beta Y+\gamma N)X \\
dH_1/dt &= \rho\beta XY - (b+\sigma+\gamma N)H_1 \\
dH_2/dt &= (1-\rho)\beta XY - (b+\sigma+\gamma N)H_2 \\
dY/dt &= \sigma H_1 - (b+\alpha+\gamma N)Y \\
dI/dt &= \sigma H_2 - (b+\gamma N)I \qquad \text{(A)}
\end{aligned}
$$

where N is the total raccoon population size ($X + H_1 + H_2 + Y + I$). The dynamic changes in the five compartments of this model are governed by the parameter values for birth rate = a, death rate = b, density-dependent mortality = γ, incubation period = $1/\sigma$, rabies-induced mortality = α, transmission rate = β, and proportion of raccoons that develop natural immunity = $(1 - \rho)$.

The qualitative predictions of this model are: (1) the first epizootic period should be approximately 48 months, (2) subsequent epizootics should occur with diminishing period (i.e., increasing frequency), and (3) epizootics should occur with decreasing amplitude. The quantitative predictions of this model, particularly the rate of diminishing period and amplitude (i.e., the rate of damping in oscillation), depend most strongly on $1 - \rho$, the proportion of infected raccoons developing viral immunity.

To match predictions from the SEIR model (A) to observed data, we constructed a phenomenological algorithm for defining when epizootics occurred, based on the time series of reports on rabid raccoon numbers by U.S. county along the eastern seaboard (Childs et al. 2000). First, for each county, the median number of reported rabid raccoons per month was determined from CDC data. Second, an epizootic was defined as beginning when the monthly number of rabid raccoons reported was greater than the county median for two consecutive months and as ending when this number was less than the county median for two consecutive months. We also required that an epizootic have a minimum duration of five months to reduce the short-term variation in reporting. We applied this algorithm to empirical data gathered through national surveillance to measure the duration of successive epizootic and interepizootic intervals, which together define the epizootic period.

Marked periodicity in rabid raccoons was apparent in many of the time series of county surveillance data (Figure 1b). The median value for the first epizootic period was 45 months, and there was a dominant mode between 41 and 60 months. The epizootic period declined by approximately five months between each successive epizootic (Figure 1c).

We then applied the same epizootic algorithm to numerical solutions to the SEIR model for different parameter sets of the SEIR. Our observed median values of 14 months for the duration of the first epizootic and 45 months for the first epizootic period fitted the predicted time series from the SEIR at the parameter set corresponding to low levels of immunity, ρ = 1–5%. Variation in the transmission rate, β, by ±25% had little effect on the quantitative structure of the model predictions. Epizootic periods subsequent to the first also were predicted to decline to about 65–80% of the first epizootic period by the fourth epizootic.

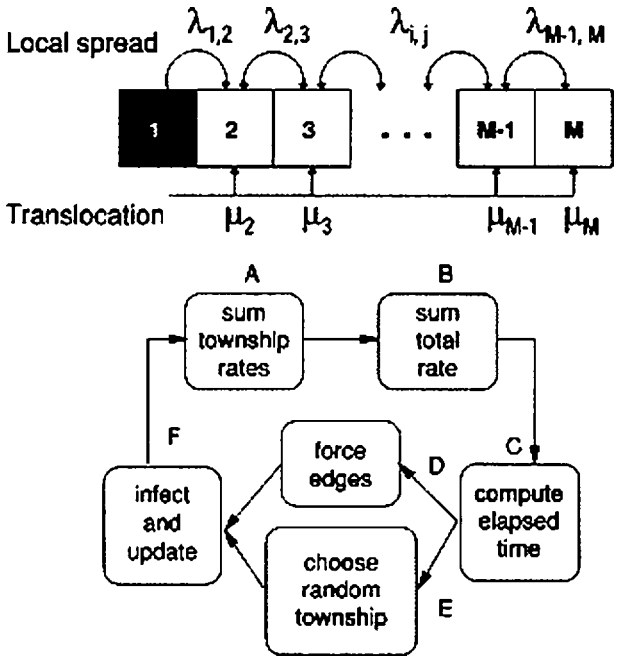

Figure 2. Schematic representation of the stochastic spatial simulator and the execution algorithm used to model the spatial dynamics of rabies virus spread. Each geopolitical unit (e.g., township, county, city, etc.) is connected locally (λ_{ij}) and globally (μ). These transmission rates can be variables and are determined by habitat and population characteristics (after Smith et al. 2002)

Our results show distinctive and predictable temporal patterning to epizootic rabies occurring among raccoons at the level of counties. The SEIR model, while capturing the local temporal dynamics of the epizootic, does not relate to predicting the spatial spread of the disease from its initial point of introduction. The second phase of our analysis was intended to build a predictive spatial model of rabies spread.

Spatial Dynamics of Epizootic Rabies

Our first strategy in developing a predictive model for rabies spread relied on surveillance data from the epizootic that swept across the state of Connecticut from 1991 through 1996. Connecticut was our first candidate data set because surveillance data indicating the time of first detection of raccoon rabies were available at the township level, leading to a twentyfold increase in spatial resolution relative to county-scale data; and, in addition, there had been a qualitative spatial analysis of the Connecticut-township data already published (Wilson et al. 1997).

We developed a discrete-event simulator (Smith et al. 2002) for which the infection of each township (i.e., rabies detected) occurred at a unique point in time. An infected township, *i*, infects its adjacent neighbor, *j*, at a rate λ_{ij}. In

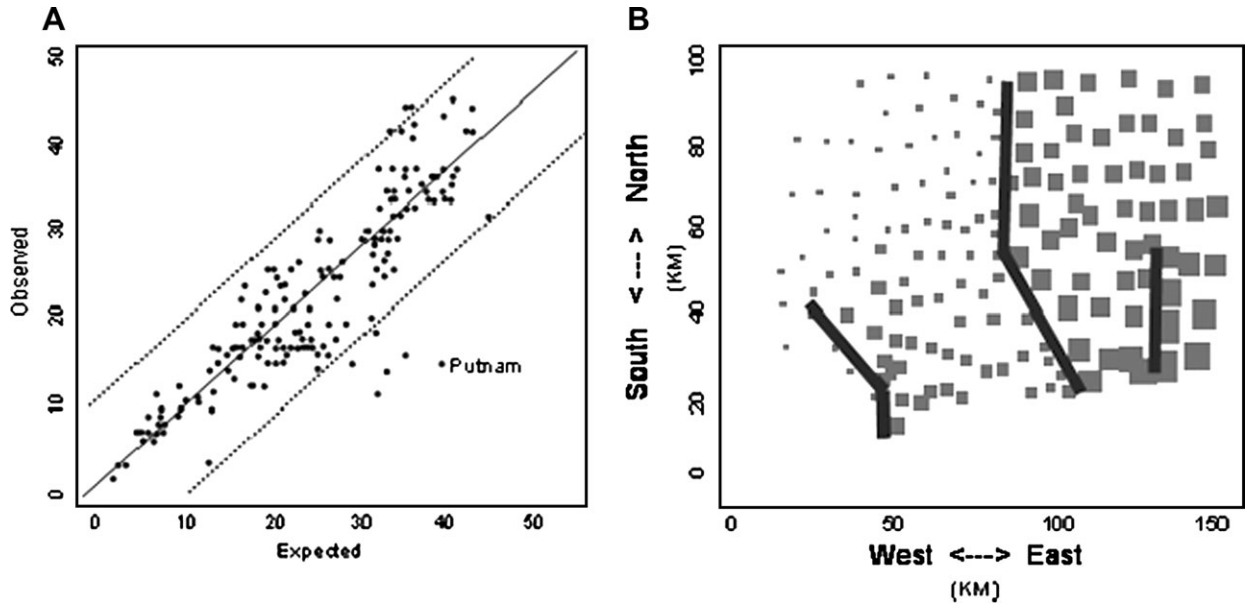

Figure 3. The data and output from the parameterized stochastic spatial simulator (Figure 2) developed to predict the spatial spread of raccoon rabies across the state of Connecticut. (A) The expected versus observed time to first appearance of rabies across the 169 townships in Connecticut. Expected time to first appearance was established using the best-fit stochastic simulator and incorporated both heterogeneity in local transmission and long-distance translocation of rabies. Rivers induced a sevenfold reduction in rates of local transmission. Four outlier townships had observed times to first appearance of rabies significantly earlier than that predicted by the model. One township in particular, Putnam, was earlier than all others and is the site of a major trash incinerator for the East Coast. Putnam may be experiencing considerable long-distance translocation of animals through the movement of trucks to the incinerator site. (B) A plot of the differential between time to first appearance across townships in Connecticut when the epidemic was simulated with and without rivers. According to the model, a sevenfold reduction in local transmission across rivers leads to an 11-month delay in the expected appearance of rabies in the southeast corner of Connecticut. The expected delay would be 16 months without long-distance translocation (after Smith et al. 2002).

addition, a township, *j*, may become infected because of translocation of rabid raccoons at a rate μ_j. Heterogeneity can be incorporated into the model by allowing the local rates from the neighbors (λ_{ij}) and the rate of translocation (μ_j) to be functions of local habitat characteristics. A schematic representation of the spatial model and the execution algorithm is presented in Figure 2.

The probability that a township remained uninfected over time was modeled as a simple stochastic decay process. The simulation algorithm used to execute this process involves six steps. (A) First, compute the total rate of infection in the *j*th township, δ_j, where

$$\delta_j = \mu_j X_j + \sum_i \lambda_{ij} X_j (1 - X_i),$$

$X_j = 1$ if the *j*th township is uninfected and $X_j = 0$ otherwise. (B) Add the township rates to compute a total rate, $\Lambda = \sum_j \delta_j$. (C) Third, compute the waiting time before a township becomes infected, assuming that waiting times are exponentially distributed. (D) Fourth, check to see if any of the edges have become infected in the elapsed interval. (E) If no edges have become infected, select a random township to infect. (F) Infect the forced edge or the infected township, update the local rates, and repeat until each township becomes infected. Forced edges correspond to those townships that establish the initial conditions for the advancing epizootic. Forced townships are not simulated; but rather, infection status is constrained to the time occurrence observed in the original data.

While we have used townships as our spatial unit, the stochastic simulator can be generalized to any spatial unit of interest. Computer code for public domain use is available at: http://medschool.umaryland.edu/departments/epidemiology/dsmith/rabies.html.

As each township becomes infected, the probability of infection in nearby townships increases. A township may become infected through local transmission if adjacent townships are infected. Local transmission rates, however, may vary, depending on local environmental conditions: for instance, vegetation type, human population density, and whether or not two townships are separated by a river. A township may also become infected through long-distance translocation of rabid raccoons. For each township, the total infection rate is the sum of the local rate, divided by the number of neighbors, plus the long-distance translocation rate.

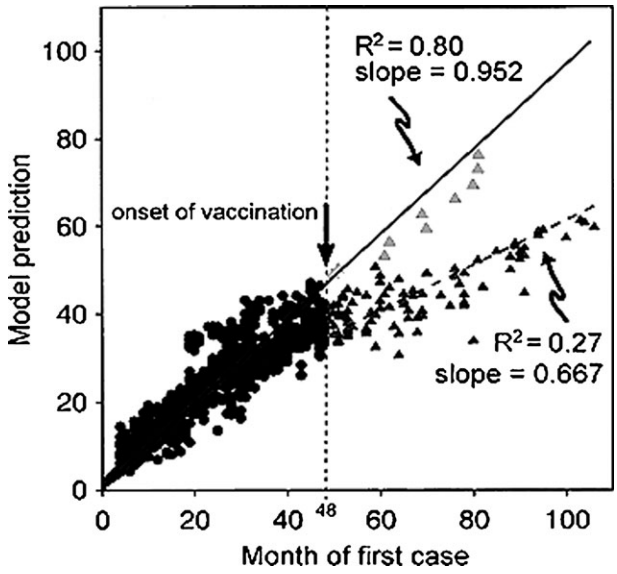

Figure 4. Relationship between model predictions and observed time to first appearance for the first 106 months of the New York epidemic. The best-fit line for the first 48 months is shown in solid black ($y = 0.9521\times$, $R2 = 0.7974$, $p < .0001$). The best-fit line after the onset of vaccination (light and dark triangles) is shown by the dashed line ($y = 0.667\times$, $R2 = 0.27$, $p < .001$). The light triangles correspond to townships in the northern portion of New York state along the Hudson River–Lake Champlain corridor. Post-vaccination townships experience a 30% reduction in rate of spread relative to that predicted by the general model (from Russell et al. 2004).

We compared the predictive power of five alternative models, where each model represented a different weighted combination of effects due to rivers, human population density, and global transport of infection. Our stochastic spatial simulator was able to mimic the spread of rabies only when environmental heterogeneity was incorporated into the model. The best-fit model (Figure 3a,b) suggested that slower local spread of rabies was strongly associated with river crossings, that the global spread by translocation was relatively frequent, and that human population density had very little effect on the local spread of rabies. In a separate study, we demonstrated how human population density influenced the magnitude of raccoon rabies epizootics but not the time to first detection (Childs et al. 2001).

Townships separated by rivers had a sevenfold reduction in local transmission. All of the models that incorporated slowing at rivers had a better fit than the alternative models without rivers. Even though local transmission accounted for most transmission, long-distance translocation was important. Of the 159 townships not on the western border of Connecticut, 21 townships (13%) recorded their first case of raccoon rabies when none of the adjacent townships were infected. All of the outlying townships (Figure 3a) identified by our model experienced rabies earlier than predicted; this was caused in most circumstances by probable long-distance translocation.

To assess the consequences of a sevenfold delay crossing rivers on the overall dynamics of rabies, we further simulated the epizootic with and without rivers and with and without long-distance translocation. Rivers delayed the appearance in southeastern Connecticut by approximately 16 months (Figure 3b) without translocation and by 11 months with translocation (Lucey et al. 2002). Environmental heterogeneities have played a significant role in determining the rate and direction of epizootic expansion of this important disease.

Predicting Disease Spread in Novel Geographic Regions

We tested the predictive power of the spatial simulator against an independent spatio-temporal data set for time-to-first-appearance of raccoon rabies across the 754 townships of New York state (Russell et al. 2003). We simulated the spread of rabies across New York using the previously derived best-fit parameters for Connecticut ($\lambda_{ij} = 0.4676$, $m_j = 0.0002944$). Using these simulation parameters, we tested the predictive capabilities of the model for the first 106 months corresponding to the available surveillance data, indicating the northernmost extent of the raccoon rabies epizootic. The model captured the dynamics of the first 48 months, but we witnessed a significant deviation away from the predicted rate of spread after month 48 (Figure 4).

After month 48, the predicted trajectory for rabies spread in the northeastern townships (Figure 4; light triangles, $y = 0.9521\times$) was similar to that of the first 48 months. However, the rate of rabies spread in townships in the northwestern portion of the state was approximately 30% lower than our model predicted (Figure 4; dark triangles, $y = 0.667\times$, $R^2 = 0.27$, $p < .001$). Month 49 corresponded with the epizootic wave front colliding with two very different spatial obstacles: townships distributing vaccine for raccoon rabies control and the Adirondack Mountains.

By 1995, the New York State Department of Health and Cornell University had begun distributing oral vaccine for immunizing raccoons against rabies (Hanlon and Rupprecht 1998) at two primary sites at the northeastern and northwestern edges of the Adirondack Mountain range in front of the advancing epizootic (C. Trimarchi, personal communication). Our observation that the average rate of rabies spread declined markedly from the predicted rate at a time and location coincident with vaccination is consistent with an interpretation of vaccine-mediated reduction in the rate of epizootic spread. However, this attractive conclusion is confounded. The coniferous forests of the Adirondack Mountains are not a preferred habitat for raccoons (Merriam 1886), and their population density in this region is extremely low (Godin 1977). The abrupt change in habitat and forest composition (coniferous forest from deciduous forest) would have a substantial effect on raccoon population densities and contact rates, which influence transmission dynamics.

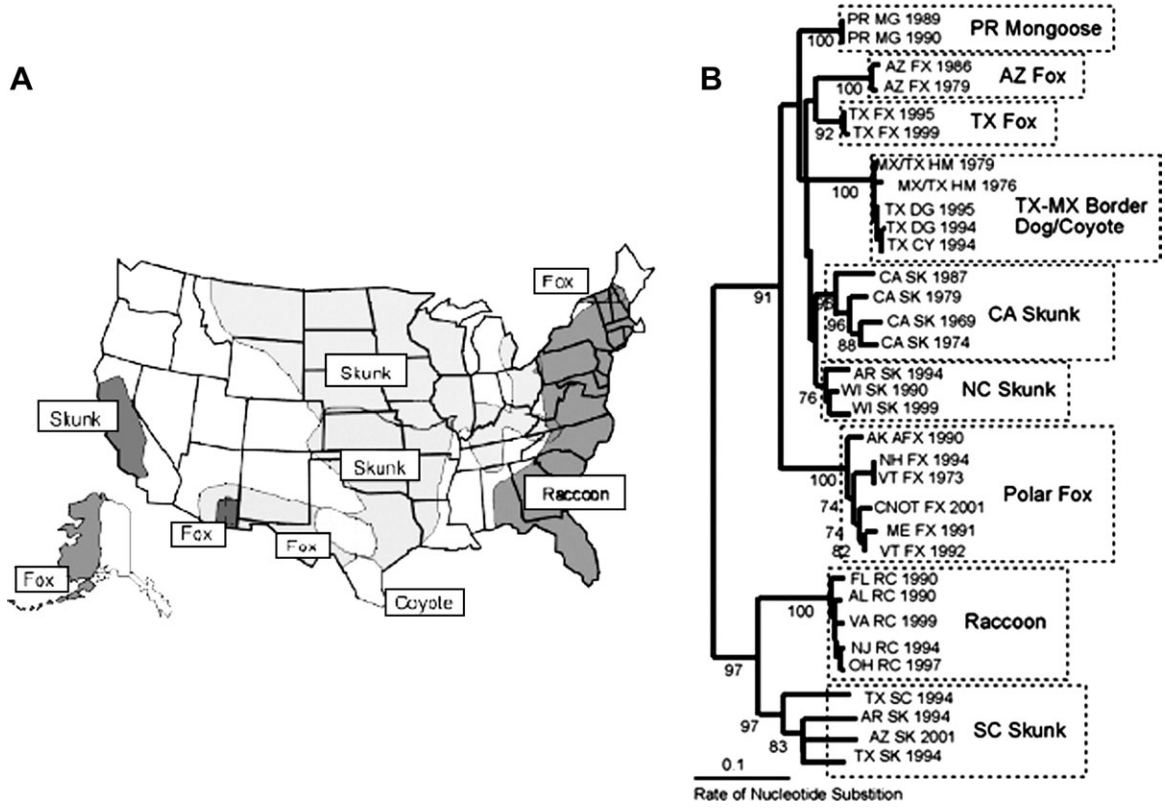

Figure 5. (A) Geographic distribution of the major terrestrial carnivore hosts of rabies virus variants. Each region is largely characterized by a unique rabies variant specific to a single carnivore host. (B) Neighbor-joining tree for nucleotide sequence of a 320-bp region of the nucleoprotein gene of selected RABV isolates from the United States, Mexico, and Canada. Each group of virus isolates that was sequenced to illustrate the unique RABV variants associated with terrestrial carnivores is boxed. The Polar Fox variant (Artic and red fox) is no longer considered enzootic in the United States. Bootstrap values are shown at the branching point for clades recovered in >700/1000 iterations of the data. ABLV was used as the outgroup and to root the tree. Samples from a rabid fox in Ontario, Canada (CN OT FX 2/4), and from two human rabies cases with exposures to rabid dogs in Mexico (MX/TX HM 1976 and 1979) are included to show variants of RABV shared across international boundaries. U.S. samples are identified by a two-letter abbreviation for the state and animal from which the sample originated, followed by the year the case occurred. With the exception of the Canadian sample (GenBank accession U11735), all RABV sequences were derived from samples in a virus repository at CDC.

Phylogeography of North American Rabies

Based on analyses of short sequences of 200 to 300 nucleotides of the nucleoprotein (N) gene, coupled with monoclonal antibody characterization, the geographic boundaries of the enzootic areas affected by different rabies virus variants circulating among terrestrial reservoir hosts in North America can be mapped with considerable accuracy (Figure 5a) (Childs et al. 2002). Various species of bats also serve as reservoir hosts for the rabies virus; however, as these volant mammals are often migratory and sufficient representative samples are available for only a few species, the geographic boundaries for chiropteran variants remain blurry (Messenger et al. 2003). As the distribution of any virus variant does not fully coincide with the full range of any terrestrial reservoir species, the potential exists for rabies variants to increase their range within current hosts. These maps serve an epidemiological function and reflect our knowledge of the geographic distribution of enzootic rabies in hosts and of the substantial degree of host specialization.

As large numbers of samples can be processed to yield information from short genomic sequences, this endeavor serves a utilitarian function of diagnostic laboratories to identify an unknown sample by matching it to the established clade delimiting the genetic variation present in a particular rabies virus variant. However, these short sequences contain an insufficient number of informative characters for accurate reconstruction of evolutionary relationships between clades and, even within the established areas of enzootic rabies ascribed to a specific variant; there is substructuring of virus populations at finer geographic scales (Figure 5b) (Childs et al. 2002). Discrete clusters of phylogenetically variable isolates of a skunk rabies virus variant can be found in California and South Carolina (Crawford-Miksza et al. 1999), suggesting early evolutionary divergence. Sequence comparisons among

isolates of the raccoon variant of rabies virus obtained from northern (New Jersey and Ohio) and southern states (Florida, Alabama, and Virginia) also indicate genetic divergence, as spatial proximity correlates with sequence similarity. In Canada, Nadin-Davis et al. (1999) have described 20 phylogenetically distinct polar fox variants of rabies virus circulating in southern Ontario, based on sequence heterogeneities in regions of the N and G genes. These 20 variants appear to cluster into subpopulations that may segregate within ecological zones or along corridors of spread.

Within a circumscribed geographic region, most rabies cases occurring among terrestrial mammals, both domestic and wildlife, are the result of infection with the virus variant circulating in the dominant wildlife reservoir host. Cross-species transmission and infection from a particular rabies variant ("spillover") occurs frequently; and although the susceptibility of a given species to a particular variant will vary, each rabies virus variant presumably retains the ability to infect the entire range of hosts susceptible to rabies. In a comprehensive analysis using monoclonal antibodies and RNA sequence analyses, 307 of 308 of the rabies virus infections occurring among dogs and cats in the United States during 1999 resulted from variants circulating in the dominant terrestrial carnivore in their county of origin (McQuiston et al. 2001); the exception was a cat infected by a bat variant of rabies virus. Similar results have been obtained for wild carnivores (Krebs et al. 2003). In very few instances is there documentation that spillover of a rabies virus variant into another species leads to sustained and independent transmission within that novel host, although several generations of transmission may occur (Daoust et al. 1996). Yet we know within historic times that successful cross-species infection by a rabies virus variant has led to sustained transmission in a novel host, generating a distinctly new and stable rabies virus variant–vertebrate host maintenance cycle; the emergence of the raccoon as a rabies host is a dramatic example.

Understanding the phylogeography of the rabies virus over time and in space is one way to explore the rate and limits of genetic variation and the ecologic and environmental features that might promote, hinder, and sustain heterogeneities in a seemingly simple genome. At a finer scale, it is unknown if the sequence heterogeneity within a particular variant population of rabies virus is driven or maintained by ecological factors or if such divergence has any epidemiological consequences. Our knowledge and long history with animal rabies provides a uniquely rich and diverse fount of information that continues to inspire and reward novel avenues of research unimaginable for any other viral zoonosis.

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