

CHAPTER 12

Spatial-temporal dynamics of rabies in ecological communities

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12.1 Background

The earliest historical records of human suffering due to infectious disease include two ancient Egyptian hieroglyphs; one depicting a man with a withered leg probably suffering from polio and another frieze depicting a man bitten by a dog and displaying symptoms of rabies (Bacon 1985). Culturally, rabies has assumed symbolic proportions representing destiny, madness, and racism. Many people are familiar with the iconic fate of *Old Yeller* and the end of mad-dog racism in *To Kill a Mockingbird*. Pasteur's development of a successful vaccine treatment for patients exposed to rabies was among the first grand successes of the Germ Theory of Disease and this success has been celebrated widely in literature and film. The 1936 Hollywood biography of Pasteur (with an Oscar winning performance by Paul Muni) has a striking scene from the period shortly after Pasteur invented his vaccine. A crowd of immigrants, all of whom have been bitten by rabid wolves on the Russian Steppe, emerge out of a fog bank and approach Pasteur's house begging for treatment. The symbolism is wonderful—out of the shrouded fog they emerge into the light of our new understanding that will bring relief and well-being! Yet despite the development of even safer and more successful treatments, better and more effective vaccines, rabies remains the most important and devastating viral zoonotic disease worldwide.

Our current understanding of the ecology and evolution of rabies virus (RABV) involves crucial inquiry into the structure and function of the virus (including aspects of its molecular organization

and pathogenesis), the potential evolution of host specialization associated with distinct virus variants, the temporal dynamics of specific host variants within specific geographic areas, and the global geographic distribution of RABV host variants coupled to patterns of spatial dynamics associated with local and regional movement of virus in infected hosts. We now turn to each of these areas of current research interest.

12.2 The virus

Rabies and rabies-related viruses are members of the *Lyssavirus* genus (Family: Rhabdoviridae) of neurotropic, single-stranded, negative-sense RNA viruses (Fig. 12.1(a)), capable of producing fatal encephalitis in a wide variety of mammalian species (Nadin-Davis 2000). Lyssaviruses are characteristically bullet-shaped enveloped viral particles consisting of a tightly associated RNA-nucleoprotein (RNP) core surrounded by trimeric glycoproteins (G) embedded within the lipid bilayer membrane of the viral envelope (Wagner and Rose 1996). The viral genome, ~12 kB in size, consists of five protein coding regions: the nucleoprotein (N), matrix (M), phosphoprotein (P), glycoprotein (G), and replicase (L) genes. The functional significance of each of the five genes has been well characterized during the replication cycle of RABV over the course of infection (Nadin-Davis 2000).

Rabies virus, the type species, serotype 1/genotype 1, for the *Lyssavirus* genus, is distributed worldwide and is endemic throughout the tropical, subtropical, and temperate regions of Africa,

North and South America, Asia, Europe, and Australia. Within regions RABV variants exhibit different degrees of host specialization and geographic compartmentalization. North American RABV variants in terrestrial carnivores show

significant species-specific geographic distributions (Fig. 12.1(b)). The classification of distinct variants of RABV to single or a few related species of mammalian hosts has been only recently appreciated and made possible through the use of monoclonal antibodies and genetic sequencing (Rupprecht *et al.* 1987, Smith *et al.* 1990, 1992; Smith and Seidel 1993). Molecular analysis of RABV suggests that geographic variants of major terrestrial carnivore hosts cluster phylogenetically within specific host lineages (Fig. 12.2(a)). Patterns of phylogenetic relatedness among viral variants are not directly related to the phylogenetic relatedness of terrestrial carnivore host species (Fig. 12.2(b)). RABV variants associated with bats, however, may show some degree of phylogenetic concordance between host and virus (Messinger *et al.* 2003).

Rabies Virus is also undergoing geographic expansion associated with three ongoing epidemics: one in Europe, one within the eastern United States, and one in Canada. The European rabies epidemic is largely associated with virus

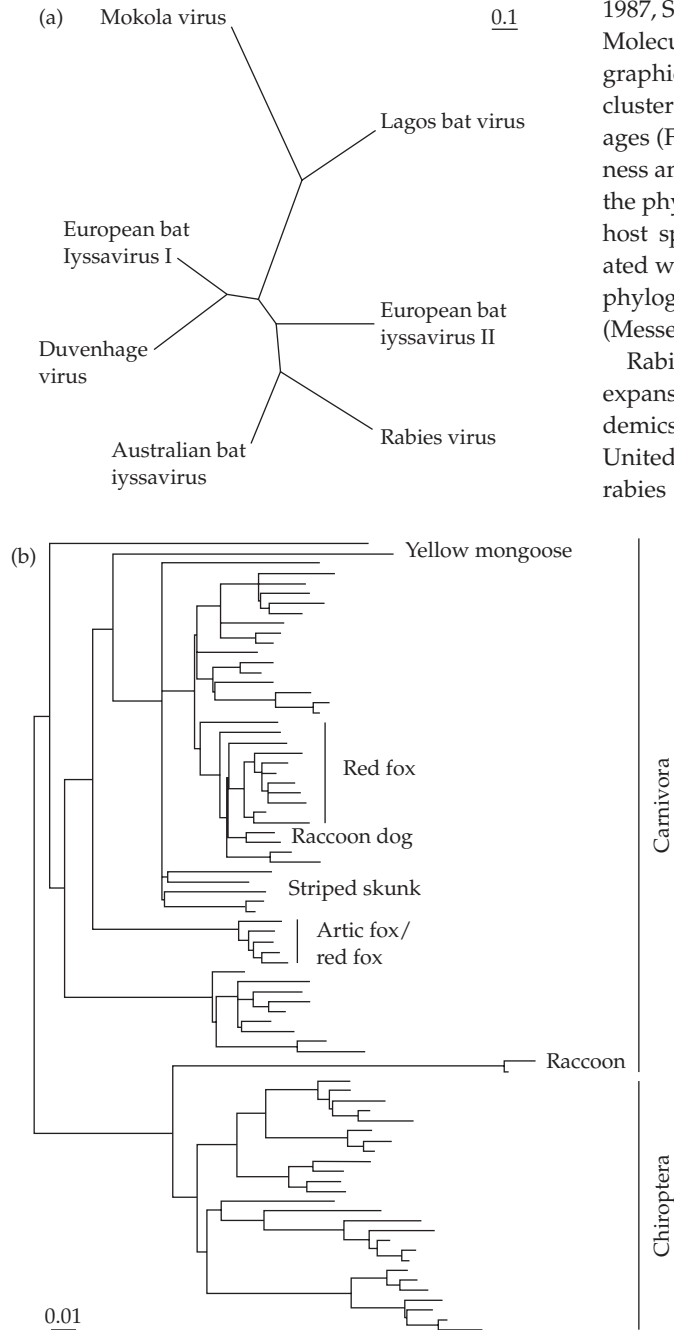


Figure 12.1 Phylogenetic relationships among rabies and other lyssaviruses. (a) Unrooted maximum likelihood tree of known lyssaviruses. Tree is based on the nucleoprotein gene (N, 1350 bp) using sequences available from GenBank and was constructed using a heuristic search under an HKY + I + G model in PAUP* 4.0b10 (Swofford 2002). (b) Neighbor-joining tree of representative rabies virus N sequences assembled from GenBank by Holmes *et al.* (2002). Carnivora sequences were obtained from domestic dogs (worldwide) unless indicated otherwise. Chiroptera sequences were collected from various North and South American bat species. Tree was again constructed in Paup* based on maximum likelihood distances calculated under a HKY + I + G model and rooted using an Australian bat lyssavirus sequence as an outgroup (not shown).

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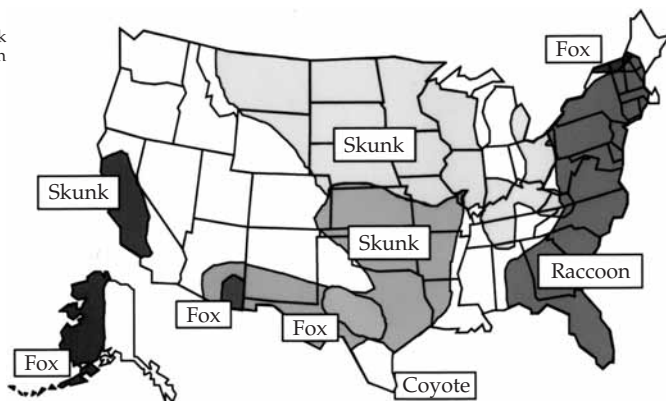


Figure 12.2(a) Geographic distribution of the major terrestrial carnivore hosts of rabies virus variants. Each region is largely characterized by a unique rabies variant specific to a single carnivore host.

spread in the red fox (*Vulpes vulpes*). The US rabies epidemic is associated with expansion of the raccoon (*Procyon lotor*) rabies variant following a presumed translocation of rabid animals from Florida to the West Virginia/Virginia border (Jenkins and Winkler 1987; Jenkins *et al.* 1998). Rabies has been endemic among raccoons in the southeastern United States for decades (Prather *et al.* 1975). The Canadian epidemic is associated with the expansion of rabies in the arctic fox (*Alopex lagopus*) into the southern provinces of Canada, especially Ontario. The southern expansion of arctic fox rabies through Canada has shifted to a red fox host after reaching Ontario. The Canadian epidemic meets the northern wave of raccoon-specific rabies expansion from the United States along the Canada/US border (Gordon *et al.* 2004). The expansion of the three epidemic waves has largely been controlled through a coordinated program of oral rabies vaccine (ORV) delivery along the front of the advancing wave (Wandeler 2000).

12.3 Global distribution of rabies virus among and affecting terrestrial mammals

No account of global rabies distribution can proceed without an introductory discussion of humans and the domestic dog. Domestic dogs serve as the major reservoir and principal source of RABV transmission to humans and other animals in many countries of Asia, Africa, and South America (WHO 1999). Other domestic and wild animals are

typically infected through secondary transmission of RABV variants maintained by dogs, or in many locations, variants of RABV maintained by wild carnivore hosts traceable to a domestic dog origin. In numerous countries of Africa, Asia, North and South America, and the Caribbean, the first historical documentation of rabies was associated with dogs transported by New World colonialists (Smith *et al.* 1992). In Asia, most of the variants of RABV described to date originated from dogs.

Prior to the arrival of European explorers and colonialists, there were no historical references to rabies in the Americas (Smithcors 1958). The first recorded outbreaks of rabies in South America, dating to 1803 in Peru and in 1806 in La Plata, Argentina, were among sporting dogs belonging to British officers (Steele and Fernandez 1991). Rabies was first recorded from Mexico in approximately 1709 and from the Greater Antilles later in the same century, in both instances first among dogs (Smithcors 1958; Steele and Fernandez 1991). Similarly, the first irrefutable report of rabies in South Africa occurred in 1893 and was traced to an Airedale terrier imported from England. However, unlike in the New World, in Africa, home to three other species of *Lyssavirus* (Lagos bat virus, serotype 2/genotype 2, Mokola virus, serotype 3/genotype 3, and Duvenhage virus, serotype 4/genotype 4), a preexisting indigenous transmission cycle of RABV was believed to predate the arrival of European dogs (King *et al.* 1994).

In Europe, terrestrial rabies has been primarily associated with a red fox reservoir for over six

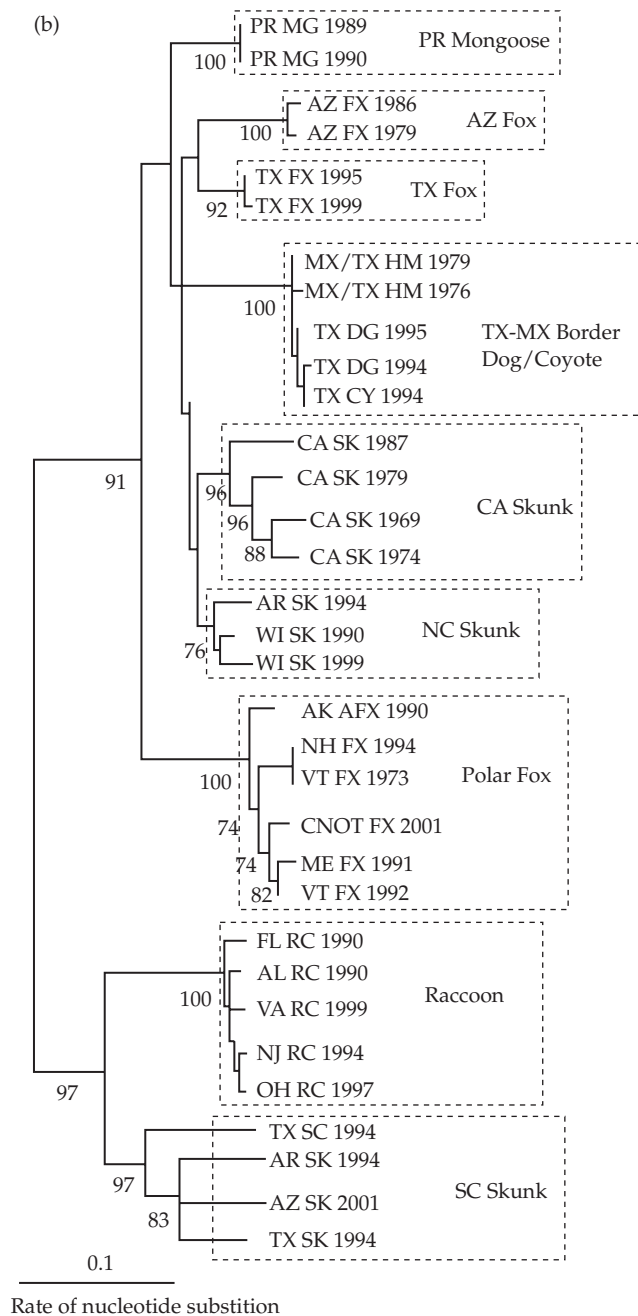


Figure 12.2(b) Neighbor-joining tree for nucleotide sequence of a 320-bp region of the nucleoprotein gene of selected RABV isolates from the United States, Mexico, and Canada. Each group of virus isolates that was sequenced to illustrate the unique RABV variants associated with terrestrial carnivores 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 points for clades recovered in > 700/1000 iterations of the data. Australian bat lyssavirus (ABLV) was used as the outgroup to root the tree. Samples from a rabid fox in Ontario, Canada (CN OT FX 2001?/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. United States 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.

decades (Wandeler *et al.* 1974a, b). However, even in Europe, evidence suggests the RABV variant circulating among red foxes had a domestic dog origin (Bourhy *et al.* 1999), as does a related, second variant of European RABV established among raccoon dogs (*Nyctereutes procyonoides*). Geographic

clustering of strains in both genetic lineages is evident in Europe, associated with physical barriers offered by rivers and mountains (Sacramento *et al.* 1992; Bourhy *et al.* 1999). The two species of European bat lyssaviruses (ELB-1 and ELB-2) have independent maintenance cycles among

insectivorous bats in Europe, western Asia, and the United Kingdom (Fooks *et al.* 2004; Picard-Meyer *et al.* 2004), and bat-associated lyssaviruses have spilled-over to cause rabies among humans and wildlife (Fooks *et al.* 2003; Johnson *et al.* 2003b; Nathwani *et al.* 2003; Muller *et al.* 2004; Tjornehoj *et al.* 2004). New species of *Lyssavirus* continue to be discovered among central European and Asian insectivorous bats (Arai *et al.* 2003; Kuzmin *et al.* 2003).

In Asia, variants of domestic dog associated RABV are the causes of human and animal rabies. Evidence exists of genetic structuring of RABV variants maintained among dog populations according to geographic location in India (Jayakumar *et al.* 2004), Sri Lanka (Arai *et al.* 2001; Nanayakkara *et al.* 2003), Thailand (Susetya *et al.* 2003), and the Philippines (Nishizono *et al.* 2002). Although RABV circulates among mongooses (*Herpestes auro-punctatus*) in some Asian countries (Patabendige and Wimalaratne 2003), the origin of the virus is presumably domestic dogs, as is also the case among mongooses introduced into the Caribbean in the 1800s to control rats (Everard and Everard 1992).

In South Africa (Nel *et al.* 1997), Zimbabwe (Bingham *et al.* 1999a, b), and Botswana (Johnson *et al.* 2004), two distinct RABV variants have been identified from specimens of over 30 different carnivore species belonging to four families of Carnivora: Viverridae, Canidae, Mustelidae, and Felidae. The two virus variants are maintained by independent cycles; one primarily associated with canids, originating with, and primarily involving domestic dogs, but also affecting several species of jackal (genus *Canis*), and bat-eared foxes (*Otocyon megalotis*); and the second cycle associated with viverrids and genets (genera *Cynictis*, *Herpestes*, *Suricata*, *Genetta*, *Civettictus*) (Nel *et al.* 1997; von Teichman *et al.* 1995). The viverrid subtype of RABV probably arose recently from spillover of the canid subtype and each of these RABV "biotopes" have crossed species barriers to infect other mammals, with no evidence of genetic modification in the virus recovered from non-reservoir host species (Nel *et al.* 1997).

In northern Africa and the Middle East, dog rabies remains the predominant threat, but wild

carnivores, notably red foxes have been involved in rabies outbreaks in Oman (Novelli and Malankar 1991), Turkey (Johnson *et al.* 2003a), and, along with golden jackals (*Canis aureus*), in Israel (David *et al.* 2000). In East Africa, spillover from RABV maintained by domestic dogs occurs among many carnivore species, including lions (*Panthera leo*) and spotted hyenas (*Crocuta crocuta*) (Cleaveland and Dye 1995; East *et al.* 2001), and poses a conservation threat for existing populations of the African wild dog (*Lycaon pictus*) (Burrows 1992; Kat *et al.* 1996) and the Ethiopian wolf (*Canis simensis*) (Sillero-Zubiri *et al.* 1996). In the West African countries of Liberia, Ghana, and Nigeria the domestic dog is still regarded as the primary reservoir host for rabies affecting humans and animals (Alonge and Abu 1984; Ezeokoli and Umoh 1987; Monson 1985); however, few wildlife studies of rabies are available from these West African countries.

In Central America and most of South America north of northern Argentina, vampire bats (*Desmodus rotundus*) and domestic dogs have long been recognized as the most important independent reservoirs for RABV (Loza-Rubio *et al.* 1999), with animal and human cases ascribed to both variants in Brazil (Sato *et al.* 2004), Trinidad (Wright *et al.* 2002), and Mexico (De Mattos *et al.* 1999). However, as wildlife studies increase in countries originally struggling with epidemic canine rabies, new associations of RABV and wildlife are being found. In Mexico, a unique variant of RABV has been described from skunks (De Mattos *et al.* 1999). Bobcats (*Lynx rufus*) were found infected with a RABV variant previously thought restricted to gray foxes (*Urocyon cinereoargenteus*) in central Arizona in the United States (Steelman *et al.* 2000). Wildlife studies in Chile have implicated the Brazilian free-tailed bat (*Tadarida brasiliensis*) as a major source of infections in domestic animals in recent decades (De Mattos *et al.* 2000). Clearly, additional chiropteran and terrestrial mammal reservoirs will be discovered for RABV and other Lyssaviruses as wildlife studies continue in countries around the world. As recently as 1999, a new rabies-like virus was recovered from a sick pteropid bat in Australia; within months of the discovery of Australian bat lyssavirus (ABLV) (Gould *et al.* 1998).

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12.4 Rabies and mammalian communities: big biases and little bodies

There are no published field data on the incidence and impact of rabies within any population of wildlife, with the exception of studies of endangered species where the appearance of rabies has threatened species already on the brink of extinction. The influence of rabies on the structure and dynamics of entire mammalian communities is nonexistent. No integrated ecological studies, with the exception of a few natural experiments, have assessed the magnitude of rabies impact on species other than medium-sized carnivores. Virtually all of the data on rabid wildlife in a geographic region are collected by national animal rabies surveillance systems. In the United States, this activity is co-ordinated by the Center for Disease Control and Prevention (CDC) and is designed to collect information to aid the prevention of disease in humans and domestic animals. As such, animal-based surveillance data provide only a crude and biased relative measure of monthly rates of rabies reported among different species, most of which are medium-sized carnivores that serve as the principal reservoir hosts for rabies virus variants to which humans and domestic animals are exposed. Unfortunately, these data are inadequate to measure or quantify rabies' impact upon any wildlife population or community process.

Nonetheless, the public health importance of rabies worldwide has generated the continuous and systematic collection of data on animal rabies, spanning more than five decades in the United States, which provides considerable information on the temporal-spatial patterns of rabies occurrence within selected wildlife hosts. The continuous, standardized collection of laboratory confirmed cases of rabies provides a dataset, irrespective of some inherent weaknesses, that can be used to explore, reveal and, through parameterization of models, predict some essential aspects of the spatiotemporal dynamics of RABV within wildlife serving as reservoir hosts.

An animal must not only survive the bite-wound inflicted during RABV transmission, but must also survive the incubation period, typically on the order of a month if rabies is to be diagnosed by methods

identifying antigen in fresh brain tissue. Therefore, surveillance counts of rabid animals should increase with the average body size of the species.

The inequality in rabies diagnoses among different sized mammals can be readily illustrated by sorting the 7970 cases of animal rabies reported in the United States in 2002 into three body-size bins. The bins chosen reflect typical average adult body-weight standards used to characterize mammalian communities (Bourliere 1975; Chew 1978); ≤ 2 kg = small, 2 to ≤ 45 kg = medium, and > 45 kg = large.

Rodents represented $<1\%$ of all species tested for rabies in the United States (Childs *et al.* 1997), and virtually all of those tested and found rabid were large species such as woodchucks (*Marmota monax*) and beavers (*Castor canadensis*). An extreme under-representation of small terrestrial mammals was obvious in this dataset. However, the factors contributing to this size-bias are confounded by reliance on human observations of suspicious animal behavior, the problems inherent to mixing small body-size with RABV transmission by bite, the financial constraints that limit diagnostic laboratories to testing only specimens from animals directly involved in a human or domestic animal exposure to RABV (Wilson *et al.* 1997), and the public health community's general assumption that rodents, with the exception of large-bodied species, carry little risk of transmitting RABV. However, rodent species examined are fully susceptible to rabies infection, can transmit RABV by bite, and have been implicated in human rabies infection (Winkler 1991). In some countries rodents have been implicated in the maintenance of RABV, but critical data to support these contentions are elusive (Okoh 1986; Summa *et al.* 1987).

Small terrestrial mammals usually account for the greatest number of individuals and biomass in any mammalian community, and potentially these populations could benefit from rabies epizootics reducing predation pressure. However, virtually nothing is known of the direct effect of rabies on small mammal populations within a community. Therefore, any discussion of the community ecology of rabies is severely limited by the profound, possibly insurmountable, deficit of any

representative information on wildlife rabies; most notably rabies among smaller mammals.

12.5 Rabies epizootic expansion

Given the public health importance of rabies, there has been a concerted effort to develop mathematical models to predict the trajectory and velocity of epizootic expansion of rabies in both Europe and North America, and often these models have been used to guide management and control strategies.

12.5.1 European red fox rabies epizootic

For reasons that are not at all clear, western Europe remained relatively rabies-free in the eighteenth and early-nineteenth centuries. The current European epizootic, primarily associated with rabies emergence in the red fox, appears to have begun in Poland sometime during 1939 and has spread westward at a relatively uniform rate of ~30–60 km per year. Red fox reach extraordinarily high densities in urban and suburban locations in Europe and these environments may have contributed to the current epizootic emergence. The current wave front stretches across Germany and most of eastern France where it has been stabilized through an ongoing wildlife control strategy employing oral vaccines whose efficacy has been optimized for the red fox host.

In a series of elegant and influential papers, Murray (Murray *et al.* 1986; Murray 1989; Murray and Seward 1992) modeled the wave front dynamics of red fox rabies as a diffusion process. In the simplest model, the fox population was divided into two groups: infectives (I) and susceptibles (S). Infectives consist of all rabid foxes and those in the incubation phase. More complex models further divide the fox population into an incubating sub-population as well as a recovered or immunized sub-population. For this simple model, however, all foxes once infected die at a rate a . The virus is transmitted to susceptible individuals at a rate r determined by the contact rate between infectives and susceptibles (rSI). Foxes are known to maintain rather fixed home ranges unless they are either rabid or young kits looking to establish a home range (MacDonald 1980), so for a non-age-structured

population model, the major spatial component will be due to the dispersal of infected animals across the landscape governed by the diffusion coefficient D km² per year. The dynamical equations for this simple system are:

$$\begin{aligned}\frac{\partial S}{\partial t} &= rIS \\ \frac{\partial I}{\partial t} &= rIS - aI + D \frac{\partial^2 I}{\partial x^2}\end{aligned}\quad (12.1)$$

Although highly simplified, this system reveals many of the important properties of the spatial dynamics of fox rabies (Murray 1989). First, there is a critical threshold for rabies persistence and rabies will die out if the fox population declines below $S_c = a/r$. Second, in regions characterized by fox population densities above the critical threshold, rabies will advance with a wave front velocity:

$$c = 2[D(rS_0 - a)]^{1/2} \quad (12.2)$$

where S_0 is the density of susceptible foxes prior to the introduction of rabies by infected foxes among neighboring populations.

Diffusion models for red fox rabies have been extended to include intrinsic population dynamics of the foxes, a sub-population of incubating infectives, and an immunized (and therefore non-susceptible) subpopulation. Addition of these biological features suggests a schematic for combined spatial-temporal dynamics of rabies, the overall features of which will be quite general (Box 12.1).

One substantial difficulty in using the diffusion model approach is incorporating habitat and environmental heterogeneity into predicting spatial dynamics. Most often we are interested in where the wave front will emerge from, rather than simply determining the average velocity of an advancing epizootic. The details of the wave front's location are often determined by small-scale environmental features that can cause the wave to bend and curl. One approach to incorporating environmental heterogeneity into a diffusion system is to assign different diffusion coefficients for sub-populations occurring within different habitats. Shigesada and Kawasaki (1997) used this approach in modeling fox-rabies spread across a

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Box 12.1 General scheme for endemic and epizootic expansion of rabies

Modeling of rabies population dynamics in raccoons using Equation (12.1) reveals many of the most salient and predictable features of epidemic expansion. These features can be generalized to almost all epidemics. Following incursion of rabies into the "uninfected zone" (Fig. 12.3), the susceptible population declines but then is followed by recurrent epizootics with declining frequency and amplitude (the enzootic phase). The first period of raccoon rabies epizootic is about 48 months and declines at a rate of

approximately 5 months per cycle thereafter. Geographic expansion of rabies occurs at a rate of about 5 km per month. The schematic is a modified form of Murray's (1989) representation of fox rabies expansion in Europe. S_0 is the density of susceptible raccoons prior to the introduction of rabies by infected raccoons among neighboring populations, and S_c is a critical threshold for rabies persistence; rabies will die out if the raccoon population declines below $S_c = a/r$ (see text).

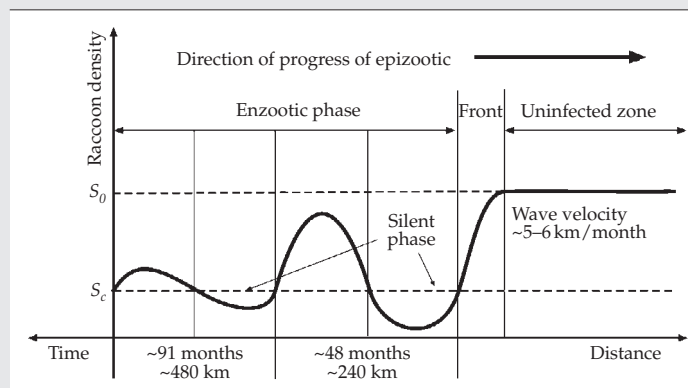


Figure 12.3 Depiction of raccoon rabies temporal dynamics, based on Murray's (1989) representation of fox rabies expansion in Europe. The diagram shows time increasing to the left of the epizootic front, and distance increasing to the right of the front.

heterogeneous landscape where there were two habitat types. Extension of this approach to multiple habitat types, however, can be very difficult.

The dynamics of spread over heterogeneous landscapes is most often influenced by local forces that are generally masked within the diffusion model structure. Alternative approaches (e.g. cellular automata, interactive networks, percolation models) construct the global spatial dynamics from explicit local (often heterogeneous) interactions. Using the North American raccoon rabies epizootic as a test system, we have used an interactive network approach to predict the spatial dynamics of rabies in raccoons.

12.5.2 North American raccoon rabies epizootic

The epizootic associated with raccoons in the eastern United States was most likely initiated in the mid-Atlantic region by the 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 RABV has spread north to Maine and Ontario, Canada, and west to Ohio (Krebs *et al.* 2003b), causing one of the most intensive outbreaks of animal rabies ever recorded. The magnitude of this epizootic was enhanced by the spread of virus through naive raccoon populations of very high density, often in states that had not experienced terrestrial rabies for decades (Rupprecht *et al.* 1995). Coincident with epizootic spread has been an increased requirement for postexposure treatment (PET) in humans. For example, in New York (NY) state the number of individuals receiving PET increased from 84 in 1989, prior to the introduction of raccoon rabies, to 1125 in 1992 and 2905 in 1993 (Anonymous 1994).

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 (CT) from 1991 through 1996 (Wilson *et al.* 1997). Using an interactive network approach

(Box 12.2), we modeled the stochastic spread of raccoon rabies across the 169 CT townships incorporating environmental heterogeneity, local transmission and long-distance translocation (LDT) (Smith *et al.* 2002). In our simulations, transport and movement of infected animals was at a smaller spatial scale than the translocation that initiated the east coast epidemic. The movement of individual animals across very great distances (such as the translocation across regions from Florida to the Virginia/West Virginia border) is very rare. However, shorter jumps well in advance of the wave-front (such as those crossing several state townships) may be quite common. In our simulations we included parameters that dictated the probability of these shorter LDT events.

We compared the predictive power of five alternative models where each model represented different weighted combinations 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 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 seven-fold 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, LDT of rabid animals was important. Of the 159 townships not on the western border of CT, 21 townships (13%) recorded their first case of raccoon

Box 12.2 Interactive network model for rabies spread

An infected township, i , infects its adjacent neighbor, j , at a rate λ_{ij} . In 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.

The probability that a township remained uninfected over time was modeled as a simple stochastic decay process, schematically represented in Fig. 12.4.

The simulation algorithm used to execute this process involves six steps. (1) 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. (2) Add the township rates to compute a total rate, $\Lambda = \sum_j \delta_j$.

(3) Third, compute the waiting time before a township becomes infected assuming that waiting times are exponentially distributed. (4) Fourth, check to see if any of the edges have become infected in the elapsed interval. (5) If no edges have become infected, select a random township to infect. (6) Infect the forced edge or the infected township, update the local rates, and repeat until each township becomes infected. Forced edges correspond to those

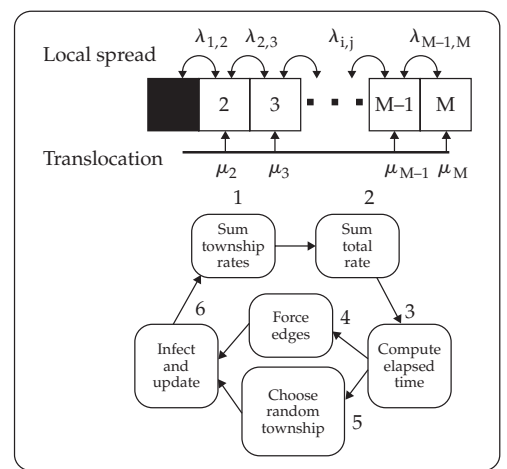


Figure 12.4 Schematic diagram of six-step simulation algorithm developed to determine the probability that a township remained uninfected with raccoon rabies over time.

townships that establish the initial conditions for the advancing epizootic. Forced townships are not simulated, but rather infection status is constrained to the date of first detection of raccoon variant rabies in the original data.

rabies when none of the adjacent townships were infected. All of the outlying townships identified by our model experienced rabies earlier than predicted probably caused in most circumstances by LDT.

The combined effects of spatial heterogeneity and LDT generate a complicated history of geographic spread. Our initial assessment, for example, does not adequately differentiate between LDT events that result in secondary foci for spread versus those LDT events that fade-out. Smith *et al.* (2005) have reformulated the interactive network model into a Network-Distance Model with different classes of LDT events and additional types of environmental heterogeneity. In our reanalysis, we found that most of the LDT events in the CT data failed to form secondary foci and that the river effect interacted with the degree of forest cover. Specifically, the effect of rivers on rates of spread was even greater when coupled with dense forest cover.

The interaction between forest cover and local transmission can lead to some direct recommendations for strategic management. In riparian areas with greater than 12% forest cover there was effectively no local transmission. Extensive riparian habitat may effectively contain the spread of rabies without vaccine intervention because these habitats are highly favored by raccoons. Once individuals have established home ranges in these habitats, they may show little propensity for dispersal and young animals may find it easier to establish new home ranges in these resource rich areas. Consequently, vaccine bait delivery might be most effective when targeted for areas of riparian habitat with less than 12% forest cover.

To assess the consequences of a seven-fold delay crossing rivers on the overall dynamics of rabies, we further simulated the epizootic with and without rivers and with and without LDT. Rivers delayed the appearance of rabies in southeastern CT by approximately 16 months without translocation and by 11 months with translocation (Lucey *et al.* 2002). We conclude that environmental heterogeneities have played a significant role in determining the rate and direction of epizootic expansion of this important disease.

We tested the predictive power of the spatial simulator against an independent spatiotemporal dataset for time-to-first-detection of raccoon rabies across the 754 townships of NY (Russell *et al.* 2004).

We simulated the spread of rabies across NY using the previously derived best-fit parameters for CT. 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 (Fig. 12.5).

After month 48 the predicted trajectory for rabies spread in the northeastern townships (Fig. 12.5, gray triangles, $y = 0.9521x$) 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 ($y = 0.667x$, $R^2 = 0.27$, $P < 0.001$, Fig. 12.5, black triangles). 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 NY Department of Health and Cornell University had begun distributing oral

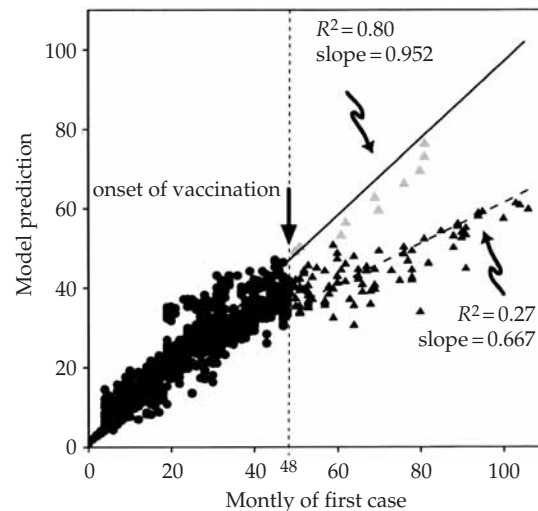


Figure 12.5 Relationship between model predictions and observed time to first appearance for the first 106 months of the New York epidemic. The best-fit line for the first 48 months (black circles) is shown by the solid black line ($y = 0.9521x$, $R^2 = 0.7974$, $P < 0.0001$). The best-fit line after the onset of vaccination (black triangles) is shown by the dashed line ($y = 0.667x$, $R^2 = 0.27$, $P < .001$). The gray 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).

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 raccoon 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.

Simulation of raccoon rabies spread into novel geographic areas can be used for more than model validation. It can be an essential tool for strategic planning and control. In late July, 2004, raccoon rabies was detected in Lake County, Ohio (OH), 11 km west of the ORV vaccine barrier along the OH and Pennsylvania (PA) border. In collaboration with the US Department of Agriculture (USDA), the State of OH, and CDC, and using the geographic locations of rabid raccoons, we simulated the likely trajectory of rabies spread across OH using the CT–NY model (Russell *et al.* 2005). The picture that emerged from several different scenarios suggests that rabies, if unchecked, will spread across the middle of the state where there are few environmental impediments or barriers. With no effective physical barriers in this region, rabies would reach the western boundary of OH in only 36 months and could travel at over 2.5 times the velocity of any previously recorded rabies epizootic. If the disease is not confined within OH the limits to raccoon variant rabies spread are defined only by the geographic distribution of its host and rabies would rapidly establish itself in raccoons throughout the mid-western United States.

Once the epizootic wave front passes through a geographic region rabies will establish itself endemically and be governed by local density-dependent dynamics (Box 12.1). The long-term

behavior of time-series of case occurrence at a given geographic location should then reveal the underlying density dependent host–pathogen population dynamics, which we address below.

12.6 Temporal dynamics within geographic locations

The temporal dynamics of epizootic rabies in red foxes in Europe was first modeled by Anderson *et al.* (1981). They constructed a simple dynamical systems model for the interaction between fox populations (partitioned into subclasses representing susceptible, infectious, and recovered/immune hosts) and rabies in a nonspatial framework. Their model accounted for many of the salient features of the temporal dynamics of red fox rabies, which includes predicting the observed 3–5 year population cycle of foxes infected with rabies, the existence of a critical threshold for local rabies epidemics, and predictions on average prevalence. They also extended the models to incorporate control strategies, that is, a mixture of culling or vaccinating foxes.

Coyne *et al.* (1989) used an analogous form of the Anderson *et al.* (1981) model to explore raccoon rabies temporal population dynamics, including an inquiry into the relative efficacy of culling versus vaccination of raccoons. They partitioned the total raccoon population into 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).

The population dynamics were governed by the following differential equations:

$$\begin{aligned}
 \frac{dX}{dt} &= a(X + I) - (b + \beta Y + \gamma N)X \\
 \frac{dH_1}{dt} &= \rho\beta XY - (b + \sigma + \gamma N)H_1 \\
 \frac{dH_2}{dt} &= (1 - \rho)\beta XY - (b + \sigma + \gamma V)H_2 \\
 \frac{dY}{dt} &= \sigma H_1 - (b + \alpha + \gamma N)Y \\
 \frac{dI}{dt} &= \sigma H_2 - (b + \gamma N)I
 \end{aligned}
 \tag{12.3}$$

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, depends most strongly on $(1-\rho)$, the proportion of infected raccoons developing viral immunity (see Box 12.1).

To match predictions from the SEIR model 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 US counties 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 ended 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 inter-epizootic intervals which together define the epizootic period.

Marked periodicity in rabid raccoons was apparent in many of the time series of county surveillance data. The median value for the first epizootic period was 48 months and there was a dominant mode between 41 and 60 months. The epizootic period declined by approximately 5 months between each successive epizootic.

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 48 months for the first epizootic period fit the predicted time series from the SEIR at the parameter set corresponding to low levels of immunity, $\rho = 1-5\%$. Variation in the transmission rate β by $\pm 25\%$ 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.

The combined use of data- and model-analysis suggests that raccoon rabies, once established in a specific spatial location, undergoes predictable damped oscillatory dynamics with a first epidemic period of approximately 48 months; the period of subsequent epizootic cycles declined by approximately 5 months per cycle. Our analysis illustrates how models when judged against data can be used to establish the most likely values of important population parameters; in our case, establishing bounds on the probability of acquiring natural immunity. Previous studies had suggested the likelihood of acquiring immunity may be as high as 20% in raccoons, but our analysis suggests that the maximum immunity expected would be $< 5\%$. We are sure that sensitivity analyses of population parameters coupling models and data will become a standard feature of future research in disease ecology.

12.7 Host population dynamics and rabies virus spillover

Our results show distinctive *and predictable* temporal patterning to epizootic rabies occurring among raccoons at the level of counties. Although models of rabies–host population dynamics were developed for a single RABV variant circulating within the specific reservoir host population, public and veterinary health officials and, increasingly, conservation biologists are most concerned about spillover of RABV to domestic animals, livestock, wildlife, and to humans. The dynamic pattern of sequential epizootic and inter-epizootic intervals predicted from the time series data from individual counties provides a qualitative measure of each county's unique history with raccoon rabies (Box 12.1). This

qualitative pattern can then be combined with quantitative values captured by national surveillance for animal rabies (Krebs *et al.* 2003a) to model the risk of rabies occurring among secondarily, and incidentally infected species (Gordon *et al.* 2004).

We developed logistic regression models to assess the risk of rabies among domestic cats as a function of the temporal stage of an epizootic within a county, the magnitude of monthly reports of rabid raccoons and total raccoons tested, and the human population size within the reporting county (Gordon *et al.* 2004). Domestic cats were chosen because they have been the domestic animal most frequently reported rabid in the United States since 1992 (Krebs *et al.* 2003a), and are responsible for many of the human PET for rabies in the United States (Moore *et al.* 2000; Moran *et al.* 2000). We included surveillance data on rabid skunks and all skunks tested for rabies as an independent covariate with raccoons. Several northeastern states, most notably Massachusetts (MA) and Rhode Island (RI), have recently reported greater numbers of rabid

skunks than rabid raccoons in their regions suggesting that skunks may serve to maintain raccoon-variant RABV transmission for a time when raccoon numbers are low (Guerra *et al.* 2003).

Our analysis included 129 counties from CT, MA, New Hampshire (NH), NY, RI, and Vermont (VT) (Fig. 12.6). After excluding cases of rabid animals infected with a red fox variant of RABV in counties along the Canadian border, we found that the risk for rabies among cats, measured as the odds ratio (OR), was strongly linked to the temporal dynamics of raccoon rabies, based on increases relative to the pre-raccoon epizootic era (defined as the time period including all months from the pre-raccoon variant interval and the pre-epizootic interval). Because the risk for rabies among cats was identical among epizootic cycles subsequent to the first, we only distinguished the components of the first epizootic cycle, epizootic and inter-epizootic intervals (Fig. 12.6). Rabies risk for cats was greatest during the first raccoon epizootic stage (greater than 12-fold the pre-epizootic level) declined to

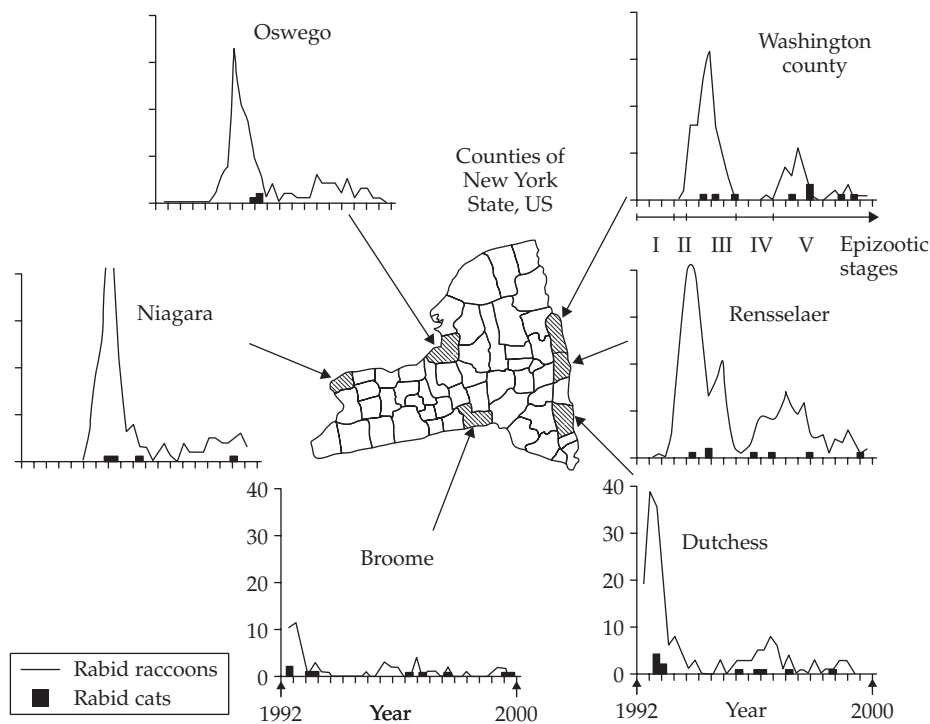


Figure 12.6 Number of raccoons and cats reported rabid at different epizootic temporal stages in Oswego, Washington, Rensselaer, Dutchess, Broome, and Niagara counties, New York (NY), from 1992 to 2000.

approximately 6-fold baseline risk into the first inter-epizootic interval, and then remained elevated at 7.5-fold baseline risk into intervals subsequent to the end of the first epizootic cycle. Independent of the temporal stage of raccoon rabies, risk for rabies in cats increased with the increasing number of rabid skunks (OR = 2.5 per 10 positive skunks). The risk for rabies among cats was significantly lowest among counties with the highest quartile of human population density and increased significantly with decreasing quartiles of human population density to 1.7-, 1.9-, and 2.5-fold the highest density quartile, indicating a pronounced urban-rural gradient. Rural cat owners are more prone to allowing their cats to roam freely in the outdoors, and large populations of stray and feral cats exist in rural areas. Unvaccinated cats from rural locations have disproportionately contributed to annual counts of rabid cats (Jenkins and Winkler 1987; Eng and Fishbein 1990).

These analyses demonstrated a strong association between risks of rabies spillover to an important secondary species and the temporal dynamics of rabies in a wildlife reservoir. The greatest risk for rabies among cats was associated with epizootics among the raccoon host, but notably, the monthly counts of rabid skunks also contributed to the logistic model outcome. There was a persistent, elevated risk for rabies among cats subsequent to the termination of the first epizootic cycle, as had been noted by descriptive studies. For example, in Maryland, the number of rabid cats did not decline over a 9-year period, even as rabid raccoon counts dwindled, but remained at relatively stable levels far higher than existed before the raccoon variant entered the state (Fogelman *et al.* 1993). The mechanism(s) for rabies spillover remains unclear, although transient transmission by skunks may play a role; there are no molecular data or epidemiologic data to suggest that host shifts have established an independent cycle of maintenance among skunks (Guerra *et al.* 2003).

12.8 Research priorities

In closing, we highlight what we believe to be the major research questions in rabies evolutionary and community ecology. The research questions are directed at each of the major subheadings above,

that is, issues relating to the virus, issues relating to spatial dynamics, temporal dynamics, and spillover and host-shift within a community context:

1. What determines the conditions under which an epidemic will originate? Are there community changes that give rise to conditions for epidemic emergence? For example, are the population densities of meso-predators, such as raccoons and foxes, influenced by the removal of top-level carnivores, such as wolves, in such a way as to increase the likelihood of rabies emergence?
2. What are the community effects of rabies? How does the rabies mediated decline in meso-predators influence the population densities and species interactions among the prey (e.g. small mammals, birds) of these meso-predators?
3. What are the major phylogeographic distributions of RABV variants and how are these distributions affected by patterns of epidemic expansion and host range distribution?
4. What is the role of long distance translocation/dispersal on patterns of epidemic expansion and phylogeographic variation at a variety of spatial scales?
5. How, and under what circumstances, do new reservoir hosts arise? For example, as dog rabies decreases in Asia and Africa, will new wildlife reservoirs emerge?
6. What are the molecular adaptations in RABV variants that promote or maintain species-specific distributions and geographic differentiation? Are there molecular correlates with novel host emergence?
7. What are the mechanisms that maintain persistence in endemic rabies? Given the high lethality of RABV, why does not it just burn out? Are communities with higher richness of potential host species more or less likely to maintain the virus?

By addressing at least this minimal set of questions, we hope to illustrate how rabies can remain a major model for understanding the ecology and evolution of host-pathogen systems in general.

Acknowledgments

We would like to thank Caroline Henderson, David Smith, Colin Russell, Lance Waller, Tracy Lambert

Jack, Susan Nadin-Davis, Roly Tinline, Chuck Rupprecht, Cathy Hanlon, and Roman Biek for their many helpful suggestions on research issues and collaboration on rabies projects. Roman Biek kindly constructed the phylogenetic trees in Fig. 12.1. This research was supported by NIH RO1 AI047498 and USDA 03 7100 4129 CA (to LAR).

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