Commentary

Raccoon rabies in space and time

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Rabies is the only pathogen to play a role in a Disney movie. While defending the children who costar in the 1957 film against a rabid coyote, the canine hero of "Old Yeller" is bitten and acquires the infection. Eventually, Old Yeller becomes rabid and moves on to the great casting kennel in the sky, and a younger understudy then helps to placate the mortified children. If Disney were to remake the film, they might have to replace canine rabies with raccoon rabies, which is now the major strain of rabies in the United States; more than 85% of the rabies cases currently recorded in the United States are reported from raccoons. Most of these are from a strain of rabies that continues to expand its geographical distribution. This rabies strain was given a new lease on life in 1976, when Jimmy Carter was elected to the United States presidency. As several members of Carter's cabinet and personal staff missed going "'coon hunting" over the weekend, they had some raccoons imported into Virginia from Georgia (1). The strain of rabies that came with these raccoons initiated an outbreak of rabies in the local raccoon population that has been steadily expanding ever since, predominantly in a northeasterly direction (2). The annual United States budget to control rabies is $300 million; a further $15 million is spent annually on postexposure prophylactic treatment of the 18,000 to 20,000 people who are exposed each year (3, 4).

Understanding the spatial spread and local dynamics of an infectious disease such as rabies is central to the design of control strategies for introduced infectious diseases. The paper by Childs (5) provides important new insights into the mechanisms that determine the rate of spread of raccoon rabies. As recently as 1997, Mark Wilson pointed out that 25 years after the current epidemic began there were still fundamental gaps in our understanding of raccoon rabies epidemiology. Centrally, there was no knowledge of how transmission occurs between raccoons, although this is widely acknowledged to be by bites, and there was a belief that significant numbers of raccoons developed immunity to infection. This was based on serology data suggesting that around 20% of raccoons test positive for rabies. The paper by Childs *et al*. (5) suggests that the development of immunity to rabies is rare in raccoons—as few as 1–5% of exposed raccoons develop immunity.

The work reported in the paper by Childs *et al*. (5) depends very much on data and information provided by the general public; it is an excellent example of "citizen science." More than 50,000 cases of rabies have been reported to the Centers for Disease Control and Prevention in Atlanta since 1980. The collation of the major subset of these data, which deal only with raccoon rabies, forms the basis for an analysis that illustrates consistent changes in the amplitude and frequency of rabies epidemics after the initial arrival of the infective wave front. In all counties where multiple epidemics of raccoon rabies have occurred, the number of reported infected raccoons in the first outbreak exceeds that in the second outbreak by a factor of three. There are then around 25% more cases in the second than the third epidemic. Concomitant with this, the interepidemic period shortens from around 45 months between the first and second epidemic to 40 months and then by an average of 5.3 months between each subsequent epidemic. This shortening of the interepidemic period would not occur if a significant proportion of raccoons developed immunity on exposure to rabies.

The epizootic of raccoon rabies has spread in a northeasterly direction at an annual rate of 30–50 km/year. Plainly, the logical next step in this work will be to produce a spatial model and to examine whether it is possible to produce a "cordon sanitaire" that might reduce the further spatial spread of the pathogen. The rate of spread is comparable to the spread of canine rabies in Europe, the current epidemic of which started in Poland at the end of World War II (6). This epidemic has been successfully controlled by using a vaccine that is introduced to the fox population through artificial food supplements (7). Specifically, chicken heads are laced with the vaccine and regularly deposited in areas where foxes are likely to locate and eat them. A significant level of success was achieved here by focusing control efforts around the mouths of mountain valleys. Fox dispersal activities tend to bottleneck into these locations, so a significant proportion of the local population may be treated while focusing the control activities into a comparatively restricted geographical location. Unfortunately, the landscape of the eastern United States is considerably less mountainous that that of central Europe. Although large rivers have slowed the spread of raccoon rabies in the northeastern United States (4), these halts have been only temporary, usually 4–8 months; raccoons are as adept as humans at using bridges. This suggests that if a vaccine becomes available, bridges might be used as bottlenecks, in the same way as valleys were used in Europe.

Before the development of a successful fox rabies vaccine, there was considerable speculation on how far rabies might spread in Europe. This speculation led to the development of a number of mathematical models for the dispersal of rabies in wildlife (see review in ref. 8). These models ranged from relatively general stochastic models (9) to more explicitly spatial deterministic models that could be used to examine the likely behavior of rabies should it enter a country with a large fox population and no previous history of rabies, such as the United Kingdom (10–11).

Several important epidemiological principles emerged from this earlier work on spatial epidemics: Murray and colleagues' pathbreaking work illustrated the power of diffusion models and led to a need to understand the dynamics of pathogens in the troughs between epidemics (10). The stochastic work of Mollison *et al*. (9) emphasized the importance of local contact processes in determining larger-scale transmission patterns. This work also identified the potential appearance of "great leaps forward," the sudden appearance of infected individuals at points well ahead of the current epidemic wave front (12). In rabies, this occurs when infected humans move animals either actively or passively. The raccoons moved to Virginia in the 1970s are a good example of the former. Detailed studies of the rabies epidemics in Connecticut and Massachusetts revealed that an occasional great leap

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forward occurred when raccoons hitched rides in the back of garbage trucks (4).

There are at least two other epizootics spreading through the wildlife of the northeastern United States. A recent paper in PNAS by Andre Dhondt and colleagues (13) reports on the impact of mycoplasmal conjunctivitis in house finches. This pathogen is spreading north and west from its point of origin in Baltimore (14), while Lyme disease continues to spread south and west from its initially reported location in Old Lyme, CT (15).

The work on mycoplasmal conjunctivitis (13–14) provides a particularly important comparison, as this pathogen is directly transmitted and produces a significant decrease in local abundance once the epidemic wave front has passed through an area. In contrast to rabies, the spatial spread of the pathogen seems to occur more rapidly, whereas the local dynamics change on a slower time scale. The faster rates of spatial spread reflect the larger distances that infected birds move, particularly on their annual migration, when birds from the northeastern United States may move as far as Texas and other parts of southern United States. The slower local dynamics presumably reflect lower transmission and virulence rates of mycoplasma when compared with rabies. Over a 2–3-year time period, these produce a steady decline in the local host abundance to around 40% of their density in the absence of the pathogen (13).

An interesting similarity between Lyme disease and raccoon rabies is that spread in a southerly direction is slower than spread in any other direction. In a recent paper in *Conservation Biology* (16), Richard Ostfeld and Felicia Keesing propose that increased biological diversity may buffer local outbreaks of Lyme disease. This predominantly occurs when the ticks that vector the pathogen waste bite on hosts in which the pathogen cannot develop. As the tick will take only a finite number of bites within its lifetime, these "wasted bites" reduce the rate of spread of the pathogen. As the diversity of "wrong" hosts increases in the warmer southern states, this effect has the potential to slow the spread of Lyme disease. But why should we observe similar slower rates of spread in the case of raccoon rabies? In contrast to Lyme disease, rabies is directly transmitted, so it unlikely that transmission will saturate. Perhaps raccoon abundance declines in the southern part of their range; this would also cause a decline in the rate of spread of the pathogen. But if this were the case, why were Jimmy Carter's colleagues dissatisfied with the quality of "'coon hunting" in the Washington, DC vicinity? Hopefully future studies of all three pathogens will allow us to address questions that examine how host species diversity effects pathogen dynamics. If other pathogens are likely to expand their geographical range in a warmer world, it will be very important to understand the role that biological diversity might play in buffering disease outbreaks.

The current state of the art in our understanding of the spatial dynamics of infectious diseases comes from Bryan Grenfell and colleagues' work on measles (17, 18). These studies build on the pioneering earlier work of Anderson and May (19, 20) and Andy Cliff *et al*., who have undertaken pathbreaking work on measles in both Iceland and the United States (21, 22). In contrast to the three cases described above, all of which occurred in situations where a pathogen has been recently introduced into a host population, measles has been present in Britain for several hundred years. Grenfell and colleagues' work has tracked the history of measles in the villages, towns, and cities of England and Wales since 1944 (23–25). The data are particularly rich, as measles is a notifiable disease in Britain; each case has to be reported to the national medical authorities by the doctor who treats it. Grenfell has collected weekly data from 1940 to the present. These data are bisected by the crucial time period in the late 1960s, when mass vaccination to control measles was first introduced. The analyses by Grenfell illustrate the importance of large-scale data sets in determining the spatial dynamics of infectious diseases. Before the advent of mass vaccination, measles was always present in Britain's larger cities: London, Birmingham, Leeds, Liverpool, and Manchester. The biennial epidemics observed in these cities spawned epidemics in the surrounding towns and villages that were too small to constantly maintain measles infection (25). A computer movie of the measles epidemics reveals waves of infection spreading out from the large cities and interfering with waves spreading from other cities. Although most of the larger cities are fairly tightly coupled together, the higher birthrates observed in Liverpool (a predominantly Catholic city) tend to keep it slightly out of phase with the other cities (25, 26).

After the advent of mass vaccination, the epidemics are less regular and more chaotic in nature (27). The large cities are less tightly coupled together, and the spatial distribution of smaller towns and villages is more important in maintaining the pathogen in the troughs between epidemics. In contrast to measles, epidemic outbreaks of pertussis (whooping cough) were more synchronized after mass vaccination (28). This is thought to be because the longer period of infection of pertussis reduces the significance of seasonal forcing before vaccination. Once vaccination was introduced in 1957, this perturbation throughout the country raised the average age of vaccination and synchronized lots of local dynamics that could then be weakly synchronized by low levels of seasonal forcing that are mainly superimposed by school terms.

Local population dynamics and spatial spread of infectious diseases are exciting areas of scientific research with important public health implications. The paper by Childs *et al.* (5) adds important detail to a larger synthesis that is emerging from studies of infectious diseases in both humans and wildlife. These studies will be become increasingly important in forecasting the spread and outbreaks of infectious diseases.

Much of my understanding of and excitement about the spatial dynamics of infectious disease comes from a lifetime of conversations with Bryan Grenfell about measles and other infectious diseases. Much of the work discussed above results from the National Center for Ecological Analysis and Synthesis (NCEAS) working group on the Spatial Dynamics of Infectious Diseases, jointly chaired by myself and Leslie Real. I have benefited significantly from discussions with all participants in this working group, which is supported through the NCEAS (supported by National Science Foundation Grant DDEB-94–21535), the University of Santa Barbara, Santa Barbara, CA, the California Resources Agency, and the California Environmental Protection Agency.

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