THERYA, 2022, Vol. 13(1):39-44 DOI:10.12933/therya-22-1183 ISSN 2007-3364

The ecology of infectious diseases: an homage to multi-factor perspectives

Richard S. Ostfeld[1]*, and Felicia Keesing[2]

[1] Cary Institute of Ecosystem Studies, Millbook. New York, 12545, U.S.A. Email: ostfeldr@caryinstitute.org (RSO).
[2] Program in Biology, Bard College, Annandale. New York, 12504, U.S.A. Email: keesing@bard.edu (FK).
*Corresponding author

Decades ago, a multi-factor perspective offered valuable insights into the causes of population cycles in arvicoline (= microtine) rodents. Multi-factor perspectives are also critical for understanding the ecology of infectious diseases. Here, we provide examples of how these perspectives inform our ability to predict variation in disease risk through space and time. We focus in particular on the evidence that many emerging zoonotic pathogens of humans have multiple hosts rather than just one, that most host species harbor more than one pathogen and that these pathogens interact, and that understanding variation in the abundance of species that transmit pathogens often requires deep exploration of the ecological community in which those hosts are embedded.

Hace décadas, una perspectiva de múltiples factores ofreció información valiosa sobre las causas de los ciclos de población en roedores arvicolidos (= microtine). Las perspectivas multifactoriales también son fundamentales para comprender la ecología de las enfermedades infecciosas. Se proporcionan ejemplos de cómo estas perspectivas dan información a nuestra capacidad para predecir la variación en el riesgo de enfermedad a través del espacio y el tiempo. Nos enfocamos en particular en la evidencia de que muchos patógenos zoonóticos emergentes de humanos tienen múltiples hospedadores en lugar de uno solo, que la mayoría de las especies hospedantes albergan más de un patógeno y que estos patógenos interactúan. Comprender la variación en la abundancia de especies que transmiten patógenos a menudo requiere una exploración profunda de la comunidad ecológica en la que están incrustados esos hospederos.

Keywords: Disease ecology; emerging infectious diseases; multifactor perspective; rodent; small mammal; zoonosis.

© 2022 Asociación Mexicana de Mastozoología, www.mastozoologiamexicana.org

Introduction

In the 1980s, Bill Lidicker proposed conceptual models to explain the semi-regular population fluctuations (aka cycles) of arvicoline (= microtine) rodents. These models invoked several potential drivers that were extrinsic to the voles themselves, including landscape structure, food supply, and predation, as well as several that were intrinsic, including aggressive behavior, dispersal dynamics, and physiological stress. He called his approach a multi-factor perspective (Lidicker 1988), and predicted that the extrinsic and intrinsic factors he invoked would vary in strength, or even appear and disappear, at different times, both seasonally and between years. The factors were also expected to interact. For instance, variation in aggressive behavior might cause changes in dispersal rates, the effects of which would depend on landscape structure (*e. g.*, the ratio of optimal to marginal patch area, or ROMPA; Lidicker 2000). Lidicker's goal was to explain a type of pattern – population fluctuations with two to five years between peaks – that varies in its specific manifestations both within and between species. The pattern of population fluctuations can vary in magnitude and timing of peaks, as well as the rate of population growth and decline. Thus, his conceptualization of the problem was holistic, in the sense that he defined "cycles" as complex and varying phenomena, and his approach to addressing the problem was also holistic, in the sense that he saw specific mechanisms interacting in complex, hierarchical ways (Lidicker 1988).

Lidicker's approach was criticized by researchers who saw arvicoline cycles as a homogeneous phenomenon rather than a variable but recognizable pattern (Gaines *et al.* 1991; Lidicker 1991). Critics with a simpler, more unitary definition of the problem developed hypotheses in which a single factor (*e. g.,* heritable aggression or specialist predators) by itself explained cycles. Such a focus was more reductionist, and usually neglected the interactions between variables. Hypotheses arising from single-factor, reductionist approaches are simpler, more tractable experimentally, and appealing for many researchers. Although critics were vociferous in the 1980s and 1990s, by the 2000s most research on arvicoline cycles incorporated multi-factor, holistic perspectives (Krebs 2013).

We were both Ph. D. students under Lidicker's guidance, Ostfeld in the 1980s and Keesing in the 1990s. Although we have both focused on the ecology of small mammals, we have paid less attention to the causes of fluctuations in population size and more attention to the consequences of those fluctuations for other ecological phenomena. Changes in the abundance of small mammals through time or across space often affect the transmission of the pathogens and parasites of those mammals. Rodents in particular are important hosts for zoonotic pathogens, those that vertebrate animals share with humans (Keesing and Ostfeld 2021).

Infectious disease ecology has its roots firmly anchored in population biology, just as arvicoline ecology does. A central question in disease ecology is what causes populations of pathogens, and the diseases they cause, to fluctuate through time or across space. As in arvicoline ecology, defining disease dynamics narrowly, *e. g*., by focusing on changes from endemic to epidemic phases, or simply by studying a particular outbreak, often elicits a search for simple explanations or hypotheses. For example, if one defines a disease system as limited to one host species and one pathogen, one will tend to seek answers in a reductionistic way, without reference to a broader context and the interactions that arise from that context. Perhaps what Lidicker called a multifactorial perspective could instead be termed an inclusive perspective, in the sense of broadening the conception of the phenomenon to be explained, as well as of the cause-effect relationships, to include the potential for complex manifestations and contingencies to play important roles. Below we describe three areas of disease ecology that we have addressed in our own research, highlighting the ways a more inclusive perspective, or Lidickerian view, helps advance understanding compared to a more traditional approach.

Replacing the single-reservoir model for most zoonoses. Broadly defined, emerging infectious diseases (EIDs) are those that are caused by pathogens that have recently evolved, recently spilled over into humans, suddenly increased in incidence, or suddenly expanded in geographic range (Morse 1995; Rosenthal *et al.* 2015). Most of the diseases of humans that are classified as emerging are caused by zoonotic pathogens. The vertebrate hosts in which the pathogens originated can be responsible for any and all of these defining aspects of emergence. Identifying the source of the emerging pathogen is expected to increase our understanding of the cause of disease emergence and suggest pathways to disease control and prevention. Consequently, much attention has been paid to determining the vertebrate source of emergence event(s).

The field of infectious disease ecology has traditionally been dominated by the "single-pathogen, single-host" paradigm, whereby it is assumed that pathogens have evolved to infect a single host species. Cross-species transmission, including transmission from a reservoir host to humans, is considered anomalous, as illustrated by use of terms like "spillover" or "species jump" to describe transmission from the focal host to some other host. Consequently, the search for the reservoir for a particular zoonotic pathogen that causes a particular EID typically focuses on identifying a single reservoir host. Such a focus is exemplified by the ongoing search for the reservoir responsible for the initial zoonotic transmission of SARS CoV-2 from some wildlife species to humans.

In reality, pathogens span a continuum of host-specificity, from those that truly infect only a single host species, to those that typically infect few species, to those that are highly promiscuous (Figure 1). Zoonotic pathogens, by definition, must infect at least two species of host – a vertebrate reservoir and humans. Pathogens that undergo a species jump from an ani-

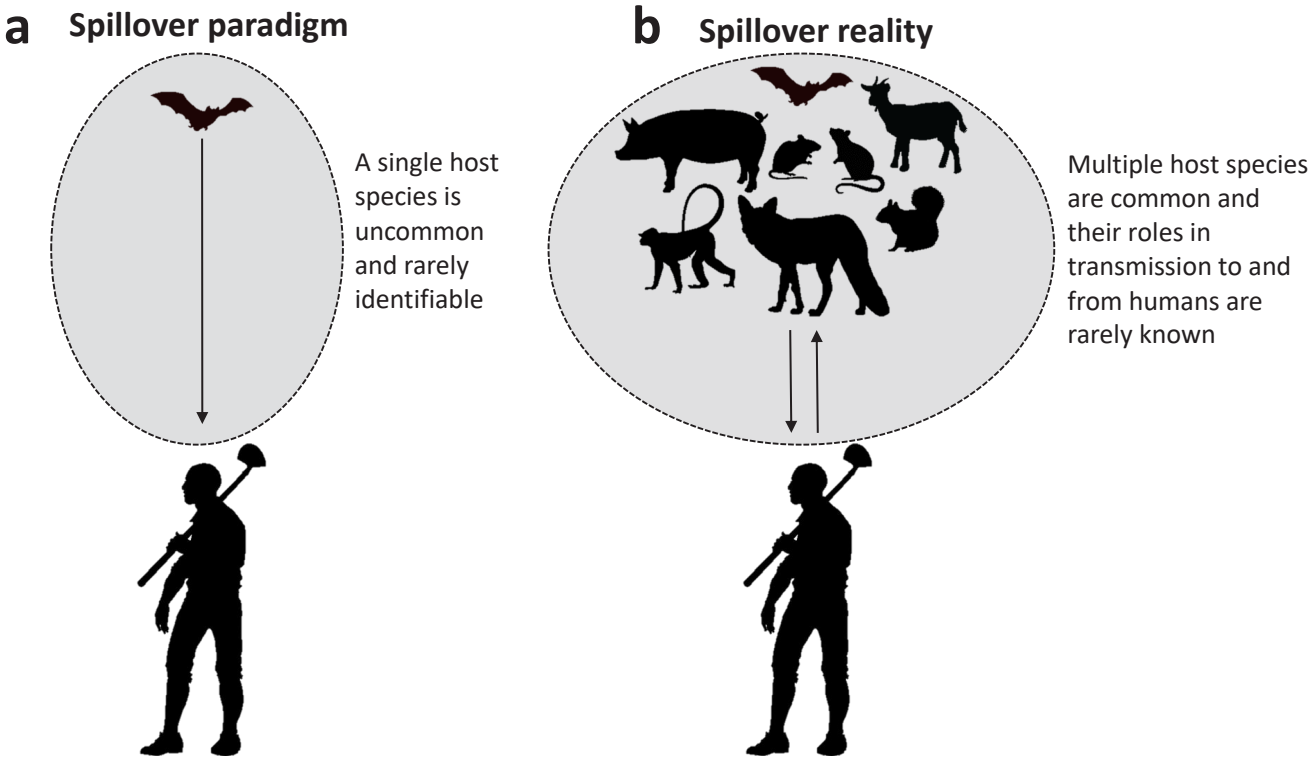

Figure 1. The paradigm (a) and the reality (b) for research on the transmission of zoonotic pathogens from vertebrate animals to humans. (a) The paradigm emphasizes a single animal host species for a zoonotic pathogen and an original spillover event, though the event and the species are rarely identified. (b) In reality, most zoonotic pathogens have multiple host species whose specific roles in transmission to and from humans are rarely known. Adapted from a figure in Keesing and Ostfeld (2021).

mal reservoir to humans tend to be more promiscuous (Keesing and Ostfeld 2021), frequently being shared with numerous host species. After all, these are the "jumpers". Occurrence in multiple species of hosts appears to be a general characteristic of the pathogens that cause EIDs in humans, and indeed, sequential infection of different host species can result in genetic changes that increase transmission to, or virulence in, new hosts, as exemplified by influenza viruses.

Focusing on a single reservoir host for a zoonotic pathogen, although appealingly simple, can be misleading and detrimental to mitigating disease. For instance, attempts to manage a reservoir host may be inefficient or even counterproductive if other reservoirs go unrecognized and unmanaged. Recognizing that multiple vertebrate species are involved in cross-species transmission of a given pathogen, including to humans, raises an inconvenient truth – that identifying pathways of zoonotic spillover involves quantifying transmission from several or many hosts rather than just one. Nevertheless, such research is likely to be critical for predicting and mitigating disease emergence (Keesing and Ostfeld 2021). A Lidickerian expansion of causal pathways is further required by the observation that some hosts play a protective role, reducing transmission rates of zoonotic pathogens by regulating abundance of pathogens (*e. g*., by absorbing but not onwardly transmitting them) or by regulating the reservoir species themselves via predation and competition (Keesing *et al.* 2009; Levi *et al.* 2012; Ostfeld *et al.* 2018; Keesing and Ostfeld 2021).

Broadening the focus to include multiple, interacting pathogens. Just as most pathogens infect more than one species of host, hosts are virtually always infected by more than one species of pathogen. Again, the reductionist adoption of a *one host-one pathogen* framework fails. There is room in such a framework to explore infection dynamics of a given pathogen as a function of a host individual (*e. g*., immune status) or of a host population (*e. g*., density), but there is no room to explore the potential effects of coinfecting pathogens. Two examples from the literature on small mammal populations illustrate the importance of explicit recognition of coinfecting pathogens within hosts.

Telfer *et al.* (2010) studied four fluctuating populations of the field vole, *Microtus agrestis*, in the UK, repeatedly taking blood samples from individual voles to track changes in the presence of the pathogens *Bartonella* spp. (transmitted by fleas), *Babesia microti* (transmitted by ticks), *Anaplasma phagocytophilum* (transmitted by ticks), and antibodies to cowpox virus (transmitted directly between hosts). Despite the potential for pathogen species within a host to interact, either directly via resource competition or indirectly via suppression or activation of immune pathways, the dynamics of pathogens have typically been addressed in isolation from each other (Telfer *et al.* 2010). Telfer *et al.* analyzed the probability of infection occurring between time steps (vole captures) for each pathogen as a function of traditional host and environmental variables, as well as of the presence of the other pathogens in the individual host.

Strikingly, Telfer *et al.* (2010) found that the presence of other pathogens generally had stronger effects on infection risk than did "factors related to exposure risk and host condition, such as age and season" (p. 244). For example, infection with cowpox virus consistently increased susceptibility to the other pathogens approximately two-fold. Voles infected with *A. phagocytophilum* were less likely to become infected with *B. microti*. And, voles infected with *B. microti* showed reduced susceptibility to *Bartonella* spp. but increased susceptibility to *A. phagocytophilum*. Telfer *et al.* argued that these four groups of pathogens (which notably constitute a subset of those infecting these voles) occur as an interaction web, affecting the host's susceptibility to other pathogens with predictably strong magnitude.

Hersh *et al.* (2014) addressed the frequency of coinfection in blacklegged ticks (*Ixodes scapularis*) in the northeastern United States with multiple tick-borne pathogens and sought to determine its cause. Coinfection in ticks with more than one zoonotic pathogen can result in simultaneous transmission of multiple pathogens to humans, with medical and epidemiological consequences. Ticks must acquire these pathogens from blood feeding on wildlife hosts, as the pathogens are not vertically transmitted. Hersh *et al.* found that coinfection of individual ticks with *B. microti* and the agent causing Lyme disease, *Borrelia burgdorferi*, was about twice as frequent as expected if the two pathogens were acquired independently (Figure 2). Moreover, they determined that ticks that had previously fed from specific small mammal hosts, especially white-footed mice (*Peromyscus leucopus*) and eastern chipmunks (*Tamias striatus*), were much more likely to be coinfected than were ticks that had fed from other hosts.

These two examples indicate that less inclusive approaches to pathogen infection in hosts and vectors – those that treat each pathogen in isolation from others – can overlook important factors driving infection risk and disease dynamics. A more inclusive approach that recognizes broader contexts is more accurate and potentially more useful for disease management.

Incorporating concepts from food webs into dynamics of pathogen and vector populations. In his paper arising from the C. Hart Merriam Award from the American Society of Mammalogists, Lidicker (1988) provided a conceptual diagram of the known and suspected factors affecting population size of voles (Figure 2 in Lidicker 1988). An inner, proximate, zone of factors included demographic processes that together produce population dynamics. The outer layers emphasized multiple drivers extrinsic to the vole population, including food resources, predators, competitors, and parasites. His conceptual model therefore subsumed several of the "single-factor" hypotheses that were ascendant at that time, including the hypotheses that time delays in the interactions between voles and their food supply (vegetation) and between voles and their predators were responsible for driving cyclic fluctuations (Krebs 2013). Lidicker's advance was to explicitly recognize that different

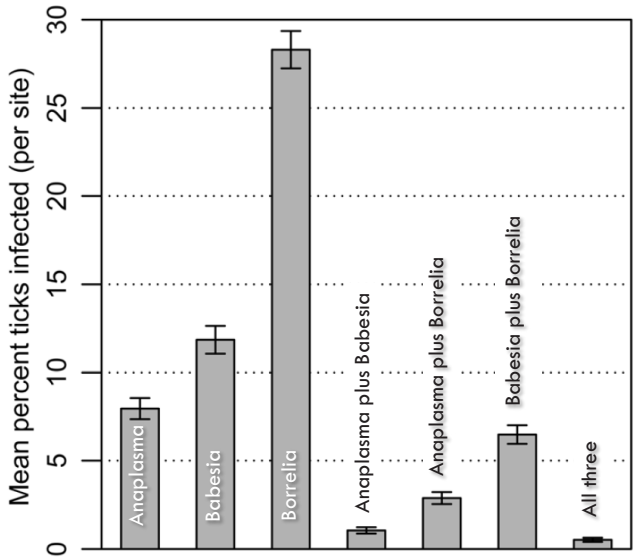

Figure 2. Mean percentage of infection for 4,368 ticks at forested sites. Ticks were coinfected with multiple pathogens more frequently than expected by chance. Each category represents the overall prevalence of a pathogen – for example, the "*Anaplasma*" bar represents not just single infections but also ticks co-infected with *Anaplasma* and either or both of the other two pathogens. Error bars represent standard error. Adapted from a figure in Hersh *et al.* (2014).

extrinsic causal pathways could operate – simultaneously or sequentially – and by acting on one or more intrinsic factors, result in a recognizable population cycle.

Much of our research in disease ecology in recent decades has focused on understanding what causes the risk of human exposure to zoonotic disease to vary in time and space. Many medical entomologists studying tick population dynamics have tended to invoke simple models in which ambient temperature and/or measures of available moisture (*e. g.*, relative humidity, vapor pressure deficit) cause patterns of tick abundance by affecting tick mortality (Sonenshine and Roe 2014). These expectations arise from extension of simple, laboratory experiments in which ticks succumb to both high and low temperatures and low humidity (Ostfeld and Brunner 2015) . Other tick experts have focused on the abundance of specific vertebrate hosts for ticks, such as white-tailed deer (*Odocoileus virginianus*), as the primary driver of blacklegged tick abundance. This expectation arises from observations of large numbers of adult blacklegged ticks on hunter-killed deer during the autumn hunting season, followed by the supposition that more deer leads to greater numbers of adult female ticks surviving and reproducing, which consequently drives population dynamics (Ostfeld 2011). Both of these simple conceptual models could be true in theory, but neither is supported by direct evidence (Ostfeld 2011), and basic natural history observations suggests they are likely to be inadequate. For example, blacklegged ticks live in environments in the upper Midwestern United States and Canada, where ambient conditions are more extreme than those that predictably kill ticks in the laboratory (Ostfeld and Brunner 2015). In addition, blacklegged ticks are extreme host generalists, parasitizing dozens of species of vertebrates within local areas, with pronounced variation in host associations between life stages (larvae, nymphs, adults; Ostfeld 2011). Consequently, strong dependence of tick population dynamics on a single host species might not be expected.

We have focused on the abundance of blacklegged ticks that are infected with zoonotic pathogens as a primary indicator of human risk (Ostfeld and Keesing 2000; Allan *et al.* 2003). Thirty years of monitoring the dynamics of blacklegged tick populations in New York State reveals that the abundance of infected nymphs is significantly correlated with the prior abundance of rodents, specifically white-footed mice and eastern chipmunks. The effect of deer abundance is weak or absent (Ostfeld *et al.* 2006, 2018). Furthermore, population density of both of these rodent species is correlated with prior abundance of acorns produced by local oak trees (*Quercus* spp.), which is an important source of food over winter (Ostfeld *et al.* 1996; Jones *et al.* 1998). Such observations lead to a multifactor model dominated by bottom-up forcing, from resources (acorns) to consumers (rodents) to parasites on those consumers (ticks and tick-borne pathogens; Figure 3). More recently, another pathway has materialized as an important contributor to tick and pathogen dynamics. Strong spatial patterns in the prevalence of infection in tick populations, whereby some tick populations have very high and others very low prevalence of zoonotic pathogens, are statistically associated with specific guilds of mammalian predators. Ticks in sites in eastern New York with diverse guilds of predators, including red foxes (*Vulpes vulpes*), raccoons (*Procyon lotor*), Virginia opossums (*Didelphis virginiana*), and striped skunks (*Mephitis mephitis*) have significantly lower infection prevalence than do sites with less diverse predator assemblages (Ostfeld *et al.* 2018). These depauperate predator assemblages appear to occur when coyotes (*Canis latrans*) supplant other predators (Levi *et al.* 2012). The diverse group of predators appears to reduce tick infection prevalence by multiple pathways, including reducing the number of rodent hosts responsible for transmitting infection (*i. e.*, the reservoir hosts), by deflecting tick meals away from rodents onto the predators, all of which are poorer reservoirs (LoGiudice *et al.* 2003), and by killing ticks directly via more fastidious grooming than occurs with the rodents (Keesing *et al.* 2009). Statistically, neither bottom-up nor top-down forces explain more than half of the variation in human exposure risk, but together they provide a predictive understanding of changing risk in space and time.

Synthesis. These studies have taken a holistic perspective to invoke multiple, interacting factors as drivers of variation in zoonotic risk. Investigating the dynamics of these complex systems sometimes requires exploring factors in isolation, *e. g.* creating an acorn pulse (Jones *et al.* 1998), while recognizing that each factor may interact with others, change in strength, experience feedback, and depend on factors outside the study system. Studying systems with so many interacting components is

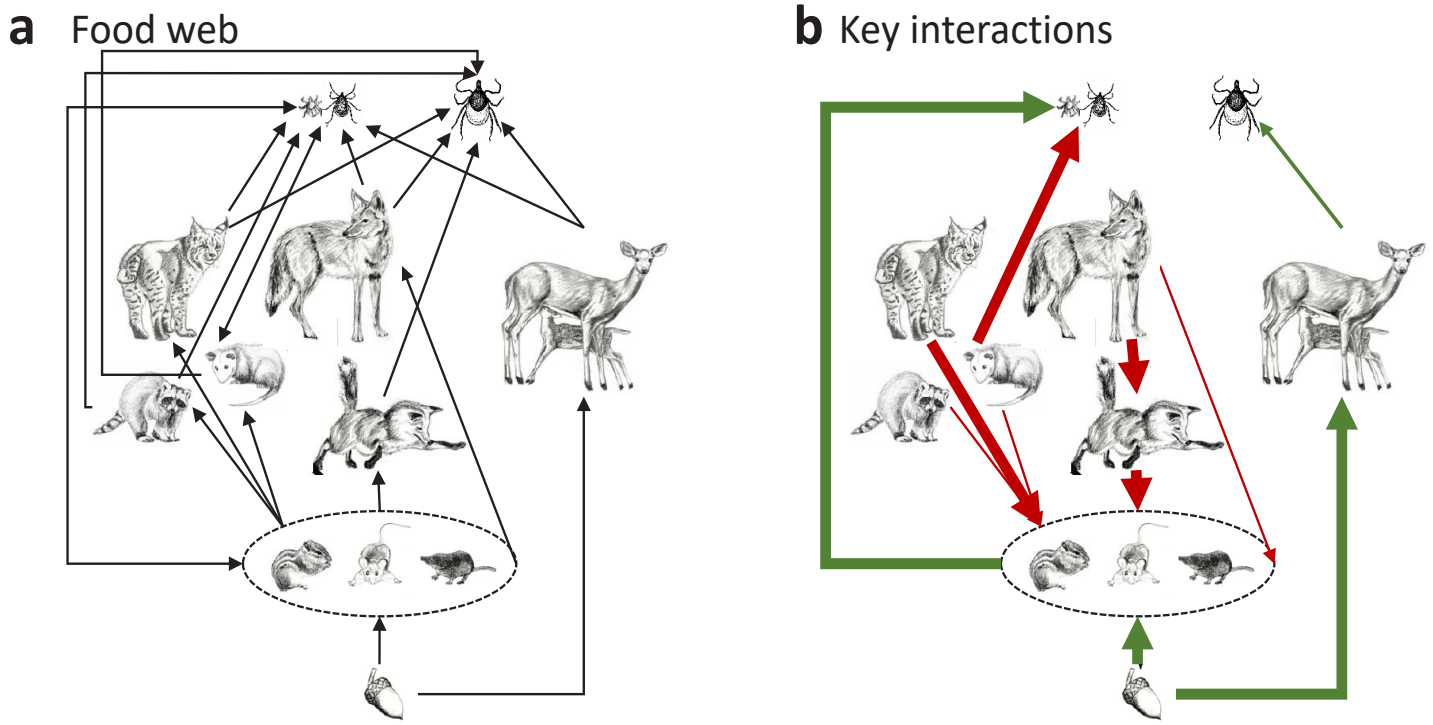

Figure 3. Webs of connections among species in the forests of eastern North America. (a) Trophic relationships, with arrows drawn from resource to consumer. (b) Key interactions, with arrow width representing the strength of relationships, and green and red representing positive and negative effects, respectively. Adapted from a figure in Ostfeld *et al.* (2018).

challenging but not intractable – these systems can be explored using experimentation, comparative or correlative approaches, and modeling. One key acknowledgment is that the very phenomena being explored may in fact be variable, showing similar patterns that are perhaps caused by different underlying processes that vary in space and time. Lidicker's multifactor approach to arvicoline population dynamics continues to inform and enlighten other research areas in ecology, including the study of infectious diseases.

Acknowledgments

We thank Ed Heske for inviting us to contribute to this wonderful volume, and doing so much to bring it to fruition. And of course we thank Bill Lidicker, who supported us both in many ways. More than twenty-five years ago, Bill even played a role in bringing us together: one of us (FK) called the other (RSO) for advice about field methods since we had an advisor in common.

Literature Cited

Allan, B. F., F. Keesing, and R. S. Ostfeld. 2003. Effect of forest fragmentation on Lyme disease risk. Conservation Biology 17:267–272.

Gaines, M. S., *et al.* 1991. A response to solving the enigma of population cycles with a multifactorial perspective. Journal of Mammalogy 72:627-631.

Hersh, M. H., *et al.* 2014. Co-infection of blacklegged ticks with *Babesia microti* and *Borrelia burgdorferi* is higher than expected and acquired from small mammal hosts. Plos One 9:9–13.

Jones, C. G., *et al.* 1998. Chain reactions linking acorns to gypsy moth outbreaks and Lyme disease risk. Science 279:1023–1026.

Keesing, F., *et al.* 2009. Hosts as ecological traps for the vector of Lyme disease. Proceedings of the Royal Society B 276:3911–9.

Keesing, F., and R. S. Ostfeld. 2021. Impacts of biodiversity and biodiversity loss on zoonotic diseases. Proceedings of the National Academy of Sciences 118:1–4.

Krebs, C. J. 2013. Population fluctuations in rodents. University of Chicago Press. U.S.A.

Levi, T., A. M. Kilpatrick, M. Mangel, and C. C. Wilmers. 2012. Deer, predators, and the emergence of Lyme disease. Proceedings of the National Academy of Sciences of the United States of America 109:10942–7.

Lidicker, W. Z., Jr. 1988. Solving the enigma of microtine "cycles." Journal of Mammalogy 69:225–235.

Lidicker, W. Z., Jr. 1991. In defense of a multifactor perspective in population ecology. Journal of Mammalogy 72:631–635.

Lidicker, W. Z., Jr. 2000. A food web/landscape interaction model for microtine rodent density cycles. Oikos 91:435–445.

LoGiudice, K., R. Ostfeld, K. Schmidt, and F. Keesing. 2003. The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. Proceedings of the National Academy of Sciences 100:567–571.

Morse, S. S. 1995. Factors in the emergence of infectious diseases. Emerging infectious diseases 1:7–15.

Ostfeld, R. S. 2011. Lyme disease: the ecology of a complex system. Oxford University Press, U.S.A.

Ostfeld, R. S., and J. L. Brunner. 2015. Climate change and Ixodes tick-borne diseases of humans. Philosophical Transactions of the Royal Society B: Biological Sciences 370:1–11.

Ostfeld, R. S., C. D. Canham, K. Oggenfuss, R. J. Winchcombe, and F. Keesing. 2006. Climate, deer, rodents, and acorns as determinants of variation in Lyme-disease risk. Plos Biology 4:1058–1068.

Ostfeld, R. S., C. G. Jones, and J. O. Wolff. 1996. Of mice and mast. BioScience 46:323–330.

Ostfeld, R. S., and F. Keesing. 2000. Biodiversity and disease risk: The case of Lyme disease. Conservation Biology 14:722–728.

Ostfeld, R. S., T. Levi, F. Keesing, K. Oggenfuss, and C. D. Canham. 2018. Tick-borne disease risk in a forest food web. Ecology 99:1562–1573.

Rosenthal, S. R., R. S. Ostfeld, S. T. McGarvey, M. N. Lurie, and K. F. Smith. 2015. Redefining disease emergence to improve prioritization and macro-ecological analyses. One Health 1:17–23.

Sonenshine, D. E., and R. M. Roe (eds.). 2014. Biology of ticks, Volume 1. 2nd edition. Oxford University Press, New York, U.S.A.

Telfer, S. *et al*. 2010. Species interactions in a parasite community drive infection risk in a wildlife population. Science 330:243–246.

Associated editor: Edward Heske
Submitted: May 24, 2021; Reviewed: July 12, 2021.
Accepted: October 4, 2021; Published on line: January 4, 2022.