OVERVIEW

Tick-borne diseases (TBDs) represent some of the world's most rapidly expanding arthropod-borne infectious diseases, yet significant gaps remain in our understanding and knowledge about them. In the United States, many tick-borne diseases such as anaplasmosis and the borrelioses, ehrlichioses, and rickettsioses are on the rise. Reasons include shifts in the prevalence and distribution of animal reservoirs and tick vectors as well as the movement of humans into areas where the animal hosts and tick populations are abundant. From a public health standpoint, the burden of disease is of growing concern, as is the incomplete understanding of the complex interactions of ticks, hosts, pathogens, and habitats that underlie changing disease patterns and the potential for climate change to exacerbate these trends.

The Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science was formed at the request of the National Institute of Allergy and Infectious Diseases to hold a 2-day workshop on the state of the science of Lyme disease and other TBDs. The committee was requested to be inclusive in the breadth of scientific approaches and disciplines, but to exclude treatment guidelines from the workshop. Furthermore, the workshop was to provide a forum for broad scientific and public input and to produce a workshop report that would highlight the major themes of the workshop and commissioned papers. The committee was not constituted to develop conclusions or recommendations. The committee recognized that the limitation of a 2-day workshop meant that not all proposed topics or speakers could be accommodated; it did its best to cover a range of topics and speakers.

The presentations summarized in this document represent the views of the individual speakers and should not be interpreted as a consensus or an endorsement by the Institute of Medicine, the committee, or its sponsors. Furthermore, the committee recognizes that the language and terminology used to describe various facets and manifestations of Lyme disease and coinfecting conditions are not uniform throughout the report—this reflects differences in scientific perspective among speakers and authors. As highlighted by many presenters, a standard lexicon that is consistently applied and understood would improve and advance research efforts related to Lyme disease and other tick-borne diseases. Furthermore, addressing the major knowledge gaps identified in this report is likely to lead to standardization of terminology as the unknown becomes the known.

The following sections of the overview summarize the committee's highlights of presentations and discussions from the scientific portion of the agenda. The committee appreciates the time and efforts of the presenters and commissioned paper authors, and the many participants who shared their stories to provide a context for these discussions. The interactions with patients and advocates were useful and constructive and served as an effective reminder of why scientific observations and gaps in knowledge need to be filled. Science is lagging behind as the burden of these diseases increase. The reader is directed to Chapter 3 for the rich presentation of participant views.

EMERGING INFECTIONS, TICK BIOLOGY, AND HOST-VECTOR INTERACTIONS

The recognized number of serious diseases transmitted by ticks has increased over the past 30 years. The emergence and increased incidence of several major TBDs has been attributed to specific human activities and behaviors that disrupt ecosystems. Increases in human population and demographic shifts have brought dramatic changes in the distribution and composition of natural habitats, as people modify the land for living spaces, agriculture, or recreation. These changes mean that people and animals interact at many more interfaces, creating new opportunities for the transmission of zoonotic pathogens, including those responsible for TBDs. This session examined the natural history of ticks and their wildlife and domestic hosts outlined the contributions of animal health experts to understanding human TBD, explored genetic diversity among pathogens, vectors, and hosts and showed how scientists are investigating the microbial community found within the ticks themselves. During the session, the individual speakers highlighted a number of research gaps and opportunities for studying TBDs. Some of these gaps and opportunities cut across individual presentations and comments from the audience. A few of the themes discussed included:

- Regional differences in the distribution of ticks and tick-borne pathogens and their contribution to human disease.
- Environmental systems and the "One Health" (i.e., the interface of human, animal, and environmental health that includes complexities of the ecosystems or the interface of biological communities and their physical or abiotic environment) approach to understanding tick-borne diseases.
- The biology and dynamic characteristics of disease vectors.
- The risk of TBDs as they relate to ecological fragmentation and reduced wildlife diversity.
- The tick microbiome and its role in transmission of pathogens to humans.

SURVEILLANCE, SPECTRUM, AND BURDEN OF TICK-BORNE DISEASE, AND AT-RISK POPULATIONS

An understanding of the science of Lyme disease and other TBDs begins with the surveillance, spectrum, and burden of disease. This session focused on the current state of knowledge of the prevalence, incidence, patterns, and severity of key TBDs in the United States and their impact on patients. The presenters discussed efforts to track the movement of pathogens in the environment, how infection moves from animals to people, and the burden of human infection and disease, especially among vulnerable populations. Some themes discussed included:

- The relative contributions of changes in surveillance, clinical recognition, and testing patterns to the rising incidence of all of the major tick-borne diseases.
- The impact of coinfection in severity of human TBDs.
- Biological understanding of persistent symptoms.

PATHOGENESIS

Understanding pathogenesis of an infectious disease at the cellular and molecular levels is critical for discovering, developing, and implementing methods to prevent infection, and to improve patient outcomes after treatment. Scientists rely on several approaches to study the pathogenesis of tick-borne diseases. These include *in vitro* laboratory studies, in vivo studies of experimental and natural infections in animals, and patient studies based on clinical trials and specimens from biopsies and autopsies. While no one approach can represent the full spectrum and complexity of human disease, the ability to "reduce" or "control" the number of variables by using in vitro and in vivo models allows more rapid and less equivocal determination of key variables in disease progression—knowledge required to improve prevention, diagnosis, and treatment of tick-borne disease in patients. This session focused on the state of the science regarding the pathogenesis of tick-borne infections—specifically those caused by pathogens in the genera *Anaplasma, Borrelia*, *Ehrlichia*, and *Rickettsia*. Themes discussed included the following:

- Research based on animal models for the testing of hypotheses related to the clinical manifestations and severity of symptoms or disease.
- The role of the immune response to tick-borne infection and its effect on bacterial load and disease manifestations.
- New technologies in animal models that explore mechanisms of pathogen persistence following antibiotic treatment.
- Translating research findings from the animal model to clinical application.

DIAGNOSTICS AND DIAGNOSIS

Diagnostics and diagnosis, which are essential to improve outcomes of tick-borne diseases, have different connotations. Diagnostics provide a cluster of objective measures directed toward identifying the cause of a disease. After scientists discover the causative agent of an emerging infectious disease, such as *Borrelia burgdorferi* or *Ehrlichia* chaffeensis, they develop, evaluate, and refine diagnostic tests over time. Diagnosis, in contrast, rests on a patient's history and symptoms and observed physical and laboratory findings in a particular epidemiologic context. Ultimately, accurate diagnosis requires knowledge of the epidemiology and clinical manifestations, as well as specific and sensitive diagnostic tests. In this session, the presenters explored the limitations of existing tests for Lyme borreliosis and other tick-borne diseases and discussed promising new approaches to diagnostics that may improve the diagnosis of these diseases, and the challenges and needs for improving initial diagnosis. Some themes discussed in this session included:

- The current status of diagnostic tests and biomarkers for TBDs.
- The role of central system sensitivity and fatigue and other sequelae, as possible biomarkers of TBDs.
- Measurement of qualitative symptoms reported by patients.
- Biorepositories for tick-borne diseases.
- Syndromic-based diagnostics for TBDs.

PREVENTION

Research efforts have been focused on ameliorating the symptoms and consequences of tick-borne diseases through treatment. However, the development, deployment, and evaluation of strategies to prevent the occurrence of tick-borne diseases were also discussed as a high priority. Prevention of infection is much more preferable to treating the short and long term consequences of disease. In this session, the presentations addressed current and future opportunities for vaccine development, the role and effectiveness of behavior change, and vector-control strategies. A few of the themes discussed in this session included:

- Research and development of safe, effective, multipathogen human and animal vaccines for tick-transmitted diseases.
- Land-use practices and public education as current tools to improve mitigation and prevention of TBDs.
- Social and behavioral considerations for TBD prevention interventions.
- Educational programs for the public.
- Assessing the impact of educational programs on patients and clinicians.

SUMMATION

The committee invited a panel of stakeholders to listen to the presentations and discussions during the course of the 2-day workshop and to share their observations regarding the research gaps and priorities in the science of tick-borne diseases. The panel members were not asked to come to a consensus, but rather to express their individual viewpoints. The panelists included a representative from a patient advocacy group, a clinician specializing in Lyme disease, a clinician–scientist specializing in *Ehrlichia* and *Anaplasma*, a clinician–scientist studying pathogenesis, and a European clinician–scientist who provided a global perspective. Following the discussion, the committee invited participants to share their thoughts. A few of the views presented during this session included perspectives on the following:

- Research funding gaps for other TBDs.
- Contribution of a national integrated research plan for advancing the science on TBDs.
- The merits of a long-term study of Lyme disease and other TBD patients.
- The role of public–private partnerships and other collaborative efforts to enhance the research on TBDs.

1

INTRODUCTION

People live in a world of growing interdependency and complexity. The old English word connexity is an appropriate description that helps to define the combination of connectivity and complexity that is our reality. Tick-borne diseases (TBDs) including Lyme disease are certainly embedded in our world of "connexity." This group of diseases defies simple cause and effect explanations and, while science has enabled us to uncover critical information on TBDs, we also realize that much more remains hidden.

TBDs represent some of the world's most rapidly expanding arthropod-borne diseases, yet we still have significant gaps in our understanding and an incomplete knowledge of them. While we can map the genome of *Borrelia burgdorferi*, the spirochete that causes Lyme disease, we still lack clarity in the natural history, epidemiology and true ecology of this pathogen as well as for other microbes involved with other TBDs. The state of the science is promising, but we lack a national, integrated research roadmap and also lack an appreciation of the process of system thinking in considering these diseases and their human impact.

Rather than focusing on a more reductionist approach to science and research, we must fully understand parts in relationship with the whole and how they influence one another. The field of complex systems is relevant to the study of TBDs. This new field cuts across traditional disciplines of science, medicine, and the social sciences. It focuses on parts, wholes and relationships. TBDs are problematic because causes and effects are not obviously related or are not closely associated in time and space. In addition, ecological knowledge has been grossly underused both to understand emerging infectious diseases and to reduce the burden of disease and mitigate its expression.

Vector-borne diseases, including diseases transmitted by ticks, continue to be a public health concern in the United States and abroad. Ticks are arthropods that belong to two large groups, hard (ixodid) and soft (argasid) ticks. Soft ticks undergo no more than seven molts during their lifecycle while hard ticks undergo three (see Figure 1-1). The life cycle duration varies as each of these life stages requires a blood meal from a vertebrate host. Ticks are highly adaptive to environmental change. In warmer climates, the life cycle duration may be less than a year. In colder climates, ticks can go months or years without feeding when the hosts are not available; the life cycle can encompass 3 years or longer. Numerous vertebrate species, such as rodents, deer, and rabbits, participate in zoonotic cycles that maintain infectious organisms in nature. Typically, a tick becomes infected with a virus, bacterium, or protozoan by feeding on an animal (reservoir host) that has the infection in its blood or by transovarial transmission of infected ova from an infected adult female tick. Ticks, in turn, transmit pathogens to reservoir animals in their salivary secretions while feeding.

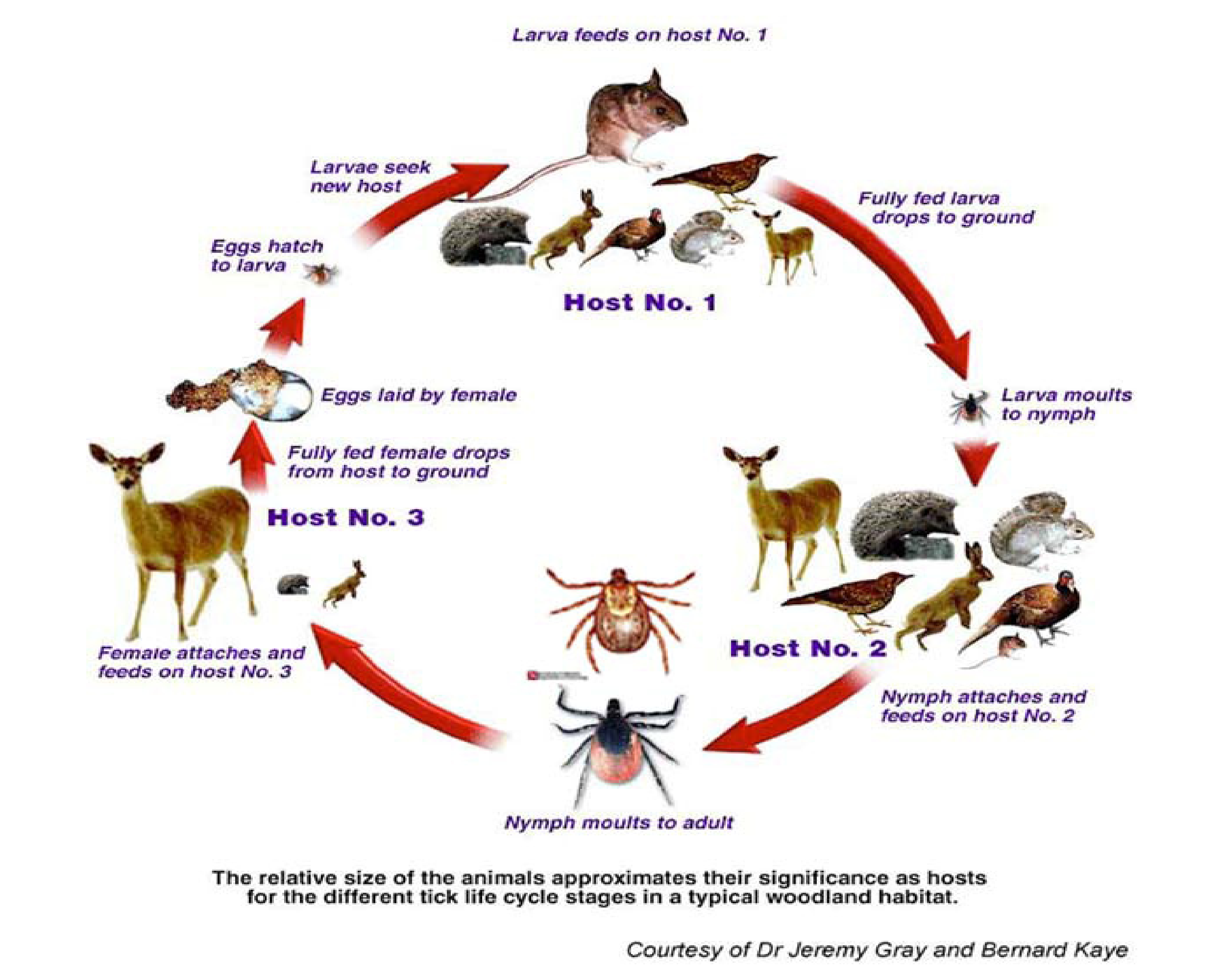

FIGURE 1-1 The life cycle of a three-host tick, such as *Ixodes* and *Dermacentor* sp., illustrating the common host for each stage. In this example, beginning prior to the first host, the eggs hatch to larvae and then feed on the first host. After the larval feeding is complete, the larvae drop from the host and molt to the nymph stage. At this stage, the nymph attaches and feeds again. It then drops off of the second host and molts to an adult. The adult tick attaches to a third host for a final meal. Following the final meal, the tick drops off and eggs laid by a female tick restarts the process.

Source: Reprinted with permission of Dr. Jeremy Gray.

This unusual lifestyle requires extraordinary evolutionary adaptation of the pathogen to the hosts, both vertebrate animals and ticks. Each of the tick-borne infections is initiated by the inoculation of the pathogen in saliva secreted by the feeding tick. Acquiring a blood meal occurs in a short feeding period only by soft ticks. Hard ticks feed for a period of days. Thus, ticks have evolved salivary components with pharmacologic activities of anticoagulation to maintain blood flow in the feeding site and modulation of inflammation and immunity to prevent deleterious host responses to the tick. The pathogen is transmitted via the tick saliva secreted during feeding (Kaufman and Nuttall, 1996), which has pharmacologically active substances (e.g., antihemostatic, vasodilatory, anti-inflammatory, and immunosuppressive) to aid in effective transmission. Infectious inocula can benefit from the local effects of the saliva, and through this transmission severe or fatal illness can result.

The local tick bite site lesion is useful for diagnosis of Lyme disease (erythema migrans) and *R. parkeri* infection (eschar). A multiple circular rash (Lyme disease); inflammation of the head and neck (tularemia); maculopapular, sometimes petechial, rash (Rocky Mountain spotted fever), and maculopapular, sometimes vesicular, rash (*R. parkeri* infection) occur frequently. Cutaneous lesions are observed less often in other tick-borne diseases in the United States.

Ticks have been recognized as a source of infections for humans for more than 100 years. In the United States, more than a dozen infectious diseases are transmitted by ticks (Table 1-1). The most common tick-borne diseases in the U.S. include Lyme disease, babesiosis, anaplasmosis, ehrlichiosis, relapsing fever, tularemia, Rocky Mountain spotted fever, and other rickettsioses. The geographic distributions of TBDs vary depending on the prevalence of the pathogen and vectors and the ecological system in which they are embedded. Additionally, tick-borne infectious diseases vary tremendously in their severity of illness. Severity of illness corresponds to visceral involvement (e.g., interstitial pneumonia and encephalitis) in Rocky Mountain spotted fever and human monocytotropic (or monocytic) ehrlichiosis. These illnesses, human granulocytotropic anaplasmosis, and tularemia can also manifest clinically as sepsis. Rocky Mountain spotted fever, however, is among the most virulent infectious diseases known, and human monocytotropic ehrlichiosis, human granulocytotropic (or granulocytic) anaplasmosis, tick-borne-relapsing fever, and tularemia are life-threatening diseases. Currently no documented cases of mortality are associated with *Rickettsia parkeri, Ehrlichia ewingii*, *and* southern tick-associated rash illness (STARI), and only very rare cases are associated with *Borrelia burgdorferi* (Kiersten et al., 2011). More than half of the tick-borne diseases in the United States are emerging infectious diseases—many of which have been recognized only in the past two decades. Given the growing list of tick-borne diseases, one would predict that there are others involving zoonotic cycles yet to be discovered.

Many TBDs such as ehrlichioses, anaplasmosis, Lyme disease, and Rocky Mountain spotted fever, are on the rise as animal reservoirs and tick vectors have increased in number and range and humans have inhabited areas where reservoir and tick populations are prevalent (Ismail et al., 2010; CDC website on statistics). From a public health standpoint, this disease trend is of growing concern. Also of growing concern is our incomplete knowledge and understanding of the complex interactions of ticks, hosts, pathogens, and habitats and potential impact of climate change. Improvements on our knowledge of this group of emerging and re-emerging diseases and their dynamics will be needed to reduce the risk of infection and the burden of these diseases.

THE GENESIS OF THE WORKSHOP

The U. S. Senate and House included in the Appropriation Bill in September 2009 the following:

> *The Committee encourages the [NIH] Director, in collaboration with the Director of NIAID, to sponsor a scientific conference on Lyme and other tick-borne diseases. The Committee believes that the conference should represent the broad*

spectrum of scientific views on Lyme disease and should provide a forum for public participation and input from individuals with Lyme disease.

TABLE 1-1 Tick-Borne Infections in the United States[1]

Disease	Agent	Vector(s)	Intracellular/ Extracellular[2]	Chronic/ Prolonged/ Acute	Life-threatening
Lyme borreliosis	*Borrelia burgdorferi*	*Ixodes scapularis, Ix. pacificus*	E	Acute >> Chronic	No
Babesiosis	*Babesia microti*	*Ix. scapularis*	I	Prolonged	Seldom
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor variabilis, D. andersoni, Rhipicephalus sanguineus*	I	Acute	Yes
Maculatum disease	*R. parkeri*	*Amblyomma maculatum, A. americanum*	I	Acute	No
Human monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	*A. americanum, D. variabilis, Ix. pacificus*	I	Acute	Yes
Ewingii ehrlichiosis	*E. ewingii*	*A. americanum, D. variabilis*	I	Acute	No
Human granulocytotropic anaplasmosis	*Anaplasma phagocytophilum*	*Ix. scapularis, Ix. pacificus*	I	Acute	Yes
Tick-borne relapsing fever	*Borrelia turicatae, B. hermsi*	*Ornithodoros turicatae, O. hermsi*	E	Prolonged	Yes
Tularemia	*Francisella tularensis*	*D. andersoni, D. variabilis, A. americanum*	I/E	Acute	Yes
Powassan/Deer tick virus encephalitis	Powassan and deer tick viruses	*Ix. scapularis, D. andersoni*	I	Acute	No
Colorado tick fever	Colorado tick fever virus	*D. andersoni*	I	Acute	Rare
Southern tick-associated rash illness (STARI)	unknown	*A. americanum*	unknown	unknown	No

[1] Worldwide, there are approximately 865 species of ticks (Keirans and Durden, 2005), of which four species, *I. scapularis*, *I. pacificus*, *I. ricinus*, and *I. persulcatus*, are the primary vectors for Lyme disease, babesiosis, and human anaplasmosis. Other tick-borne illnesses that may occur in the United States include *Rickettsia* sp. 364D strain carried by *D. occidentalis* on the Pacific coast, *E.muris*-like organisms in the upper midwestern states, *Babesia duncani*, and *B. divergens*-like infections. The most frequently imported travel-associated tick-borne illness is African tick bite fever caused by *R. africae*. *Rickettsia massiliae*, a potential human pathogen, has been identified in *Rh. sanguineus* ticks in the United States, but not yet in humans. *Coxiella burnetii*, the agent of Q fever, occurs in ticks, but transmission in the United States is associated with inhalation of aerosols from animal parturition.

[2] E=extracellular; I=intracellular

In March 2010, the National Institutes of Health (NIH) and the National Institute of Allergy and infectious Diseases (NIAID) contracted with the Institute of Medicine to form a committee to plan the workshop and summarize the viewpoints in a workshop report. NIAID charged the committee to hold a workshop that discussed the state of the science, but that did not include a discussion of treatment guidelines. The committee was to provide opportunity for public input into the activity.

THE COMMITTEE APPROACH

The Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science met on April 29, 2010 in a planning session that was open to the public. Federal agencies conducting research in the field were invited to make brief presentations to the committee. These presentations were followed by a public comment period, during which interested members of the research, advocacy, and patient communities were invited to make brief remarks. Individuals also were encouraged to submit comments to the project's e-mail address.

Following the initial meeting, the committee decided that it needed to provide additional opportunities for input from patients and groups not represented by the individuals who attended the planning meeting. The committee held four listening sessions on June 2, 15, 18, and 25, 2010, to hear from residents of the Southeastern United States (Georgia, North Carolina, South Carolina), the Southwest and West (Arizona and California), the Midwest (Michigan, Iowa, Wisconsin, and Minnesota), and members of the Native American population, respectively. The publicized target populations served as guidelines for those registering for the listening sessions, and the committee did not exclude anyone who wished to register but did not fit into one of the groups. A multiplicity of viewpoints with diverse ideas for workshop topics and speakers were expressed in the listening sessions, e-mail submissions, and planning meeting. Appendix C summarizes the public input into the agenda of the workshop.

The committee recognized the limitation of a 2-day workshop, which meant that not all proposed topics or speakers could be accommodated. The development of the agenda was driven primarily by topics that would cover the state of the science in tick-borne diseases: surveillance, burden of disease, diagnosis, diagnostics, at-risk populations, environmental and host interactions, pathogenesis, and prevention, as well as the human face of the disease. Per NIAID's charge to the committee, discussion of treatment guidelines was excluded from the workshop. With any complex scientific discipline it is difficult to limit discussion on a disease without some references to treatment. The committee further excluded the topics of physicians' discipline by state medical boards and insurance reimbursements from the workshop. Although these topics are of concern for many patients and clinicians, they fell outside the scope of the state of the science.

In addition to the speaker presentations, the committee commissioned 10 papers to gather further information on the state of the science of tick-borne diseases. The papers address a number of areas, including diagnostics, emerging infections, tick-transmitted microbes, vaccines, environmental contribution to tick-borne diseases, atypical Lyme disease, global burden of disease, case definitions, and a patient perspective. The patient perspective paper addresses the human aspect of tick-borne diseases. All of the commissioned papers are included in Appendix A. The Committee also requested information from Federal agencies that conduct research or have programs associated with tick-borne diseases in their current research programs on tick-borne diseases. The information is summarized in Appendix B. Finally, the Committee recognized that even with a generous allotment of time for discussion, a number of comments would not be able to be expressed during the workshop. The additional comments sent to the Committee by e-mail are summarized in Appendix E.

Upon reviewing the presentations and comments during the workshop and in the pre-workshop listening sessions, the committee acknowledged that the language and terminology used to describe various facets and manifestations of Lyme disease and coinfecting conditions are inconsistently applied. Rather than offering its own interpretation of terms and definitions used by the various presenters, the committee has transcribed the terms as they were used by the workshop participants. This does not imply that the committee believes that terms such as "post-Lyme disease," "post-treatment Lyme disease," "persistent Lyme disease," and "chronic Lyme disease" are or are not interchangeable, differ in meaning or value, or have differing scientific validity. Similar confusion exists regarding terminology related to recurrent and relapsing Lyme disease with or without reinfection. As highlighted by many presenters, a standard lexicon that is consistently applied and understood would improve and advance research efforts regarding Lyme disease and other TBDs and likely improve patient care.

This workshop summary report is a reflection of what occurred during the workshop held on October 11–12, 2010. As part of the charge, the committee invited individuals with diverse viewpoints to present and participate at the workshop. The committee recognizes that not all viewpoints to fully discuss the nuances of the state of the science were represented at the meeting, nor with the number of topics areas, could a point–counterpoint discussion occur. This workshop was designed to not reach concensus, but discuss a range of ideas. The committee did not weigh the scientific evidence on any topic, but did ask the presenters to supply the references for their remarks. Where the references were available, they were included. Furthermore, the summary report should not be interpreted as a consensus of the Institute of Medicine, the committee, or its sponsors. The views presented, including the key knowledge gaps and research opportunities, are those of the individual speakers.

The reader will note that the workshop report is organized into eight additional chapters, which summarized the Committee's preliminary introductions to the respective chapter and the corresponding presentations. The presentations from speakers and sessions may be presented in a different order than that reflected in the agenda. Chapter 2 provides a broad overview of tick-borne diseases from a systems perspective. Chapter 3 provides the societal and patient perspective of Lyme disease. Chapter 4 reflects the ecology, tick biology, and host interactions discussions. Chapter 5 provides a broad overview of the surveillance, spectrum, and burden of tick-borne diseases. It further includes a discussion of at-risk populations. Chapter 6 reviews the latest research on pathogenesis of four tick-borne diseases: Lyme disease, anaplasmosis, ehrlichioses, rickettsial diseases. Chapter 7 reviews the state of the science on diagnostic tools for tick-borne diseases and the challenges for physicians in the treatment of these diseases. Chapter 8 provides a short overview of the prevention, including vaccines and non-pharmaceutical measures. Chapter 9 summarizes the viewpoints from participants on the research gaps, opportunities, and priorities for the field of tick-borne diseases.

2
An Overview of Tick-Borne Diseases

A SYSTEMS APPROACH TO UNDERSTANDING TICK-BORNE DISEASES: PEOPLE, ANIMALS, AND ECOSYSTEMS

Richard S. Ostfeld, Ph.D., Cary Institute of Ecosystem Studies

Throughout the 20th and 21st centuries, the number of infectious diseases in humans has been increasing as approximately 335 human infectious diseases have emerged since 1940 (Jones et al. 2008; Figure 2-1). Approximately 60 percent of those diseases are zoonotic, of which 72 percent are transmitted from wildlife and the remainder are transmitted from domestic animals. Furthermore, approximately 30 percent of emerging infectious diseases are vector-borne, which include tick-borne diseases (TBDs). Currently, there is incomplete and inadequate knowledge about key factors pertaining to persistence of reservoir, transmission, and host responses. More research is needed to better understand these diseases and to improve strategies to protect human health.

Lyme disease, one of the tick-borne diseases in the United States, emerged in the later half of the 20th century. It was first described in United States in the mid-1970s, although cases were reported in Europe in the late 1800s and early 1900s. The annual incidence of reported cases of Lyme disease has grown significantly from its initial recognition through 2008. By 1982, the Centers for Disease Control and Prevention designated Lyme disease as a notifiable disease, but even with this designation, an unknown number of cases remain unreported. Lyme disease is also found in Europe, where it is one of the fastest growing zoonotic diseases.

Reducing the burden of Lyme disease and other TBDs requires two main strategies: treatment of currently infected patients and prevention of transmission. Prevention is the ultimate goal to reduce the number of infections and clinical manifestations of TBD. Critical to any prevention measure is a fundamental understanding of the tick, its hosts, the pathogen and the dynamic interplay of these components. Armed with that understanding, we can target the life stages, habitats, and other features of the organisms that confer a high risk of Lyme disease and other TBDs. Because effective vaccines are not currently available to humans, prevention strategies can be grouped into two approaches. The first focuses on human behavior such as the use of repellants and protective clothing, avoidance of risky activities and habitats, and so forth. The second is environmental and includes interventions that target ticks, their hosts, and the pathogens they transmit.

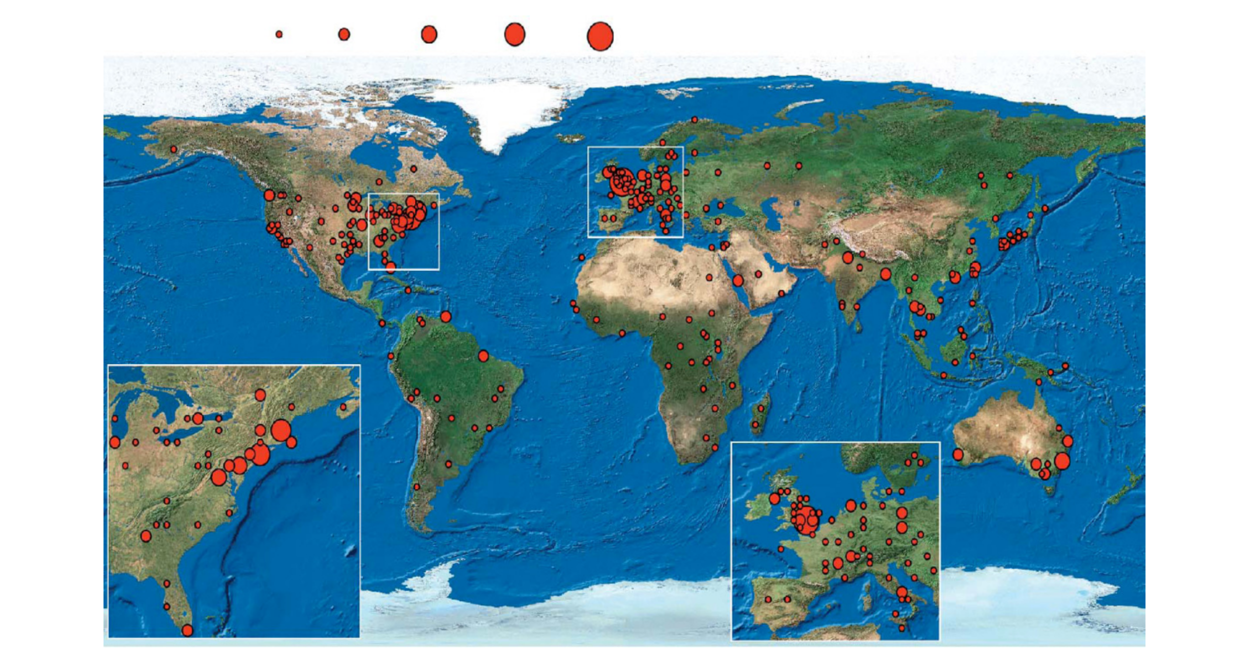

FIGURE 2-1 Global richness map of emerging infectious diseases from 1940 through 2004 showing clustering in the northeastern United States, western Europe, Japan and southeastern Australia.
SOURCE: Jones et al., 2008.

In most of Northeastern United States, the black-legged tick, or *Ixodes scapularis*, is the primary vector for the transmission of *Borrelia burgdorferi,* the spirochete bacterium that causes Lyme disease. The *Ixodes* tick is a three-host tick, and its life cycle includes three post-egg stages: larva, nymph, and adult. At each stage, the tick takes a single blood meal from a vertebrate host. The tick then drops off the host and molts into the next stage: larvae into nymph, nymph into adult (see Figure 2-2). After a single blood meal during which the males and females copulate, the adults also drop off, the females lay eggs, and both adults die to complete the life cycle.

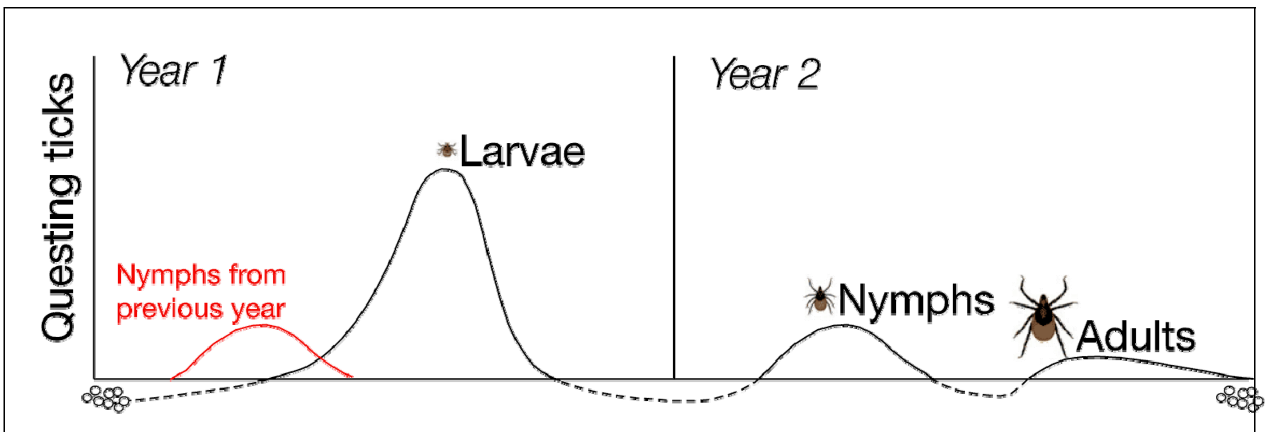

FIGURE 2-2 In its 2-year life cycle, the black-legged tick develops from egg to adult, taking a single blood meal at each stage in its development.

SOURCE: Unpublished, reprint courtesy of Dr. Brunner.

Larval ticks hatch uninfected with Lyme disease spirochetes because of the lack of transovarial transmission of the pathogen from ticks through their eggs. However, the larval ticks will feed on virtually any warm-blooded vertebrate they encounter while questing on the forest floor. If they happen to feed on a host infected with Lyme disease spirochetes, the larvae may become infected. In that case, they will molt into an infected nymph capable of transmitting the infection to its next host, including humans.

Lyme disease and other TBDs are most likely to be transmitted to humans during the nymphal stage. The primary reasons are the frequent high prevalence of infection among nymphal ticks, the very small size of the nymphs, and the fact that nymphs reach their peak activity in late spring and early summer when human outdoor activity also peaks. The size of the nymphal population peak and the prevalence of infected nymphs are critical in determining the risk of human exposure to Lyme disease and other TBDs.

After Lyme disease was discovered in the 1970s, conventional wisdom held that only a few hosts determine how many infected nymphs would appear in a given year, with white-tailed deer being the predominant one. Even today, many research articles suggest that white-tailed deer are the definitive host of the black-legged tick. This theory is true for some environments[1]. For example, in a recent study on Monhegan Island, Maine, Rand and colleagues (2004) hunted to reduce a deer herd from approximately 100 to zero in a few years. By the end of the study, larval and nymphal tick populations had also declined to near zero. However, this is likely because humans and their pets were the only host species available on the island for adult black-legged ticks after the removal of the deer.

Other studies that have controlled deer populations and monitored tick populations have found a different outcome when other host species for the black-legged tick were present. For example, Stafford et al. (2003) significantly reduced a deer herd at two sites in southern Connecticut. At one site, the nymphal tick population declined steadily, and the researchers found a significant correlation in the size of the deer and nymphal tick populations. However, they found no significant correlation between deer and nymphal tick populations at the other site. Similarly, Deblinger et al. (1993) reduced the deer population on the northern coast of Massachusetts by 40 percent per year. Initially, the nymphal tick population declined significantly. However, by the end of the study the nymphal tick population had recovered and returned to the population level at the beginning of the study. Other studies have found no correlation between deer density and nymphal tick density in New York (Ostfeld et al., 2006) or between deer density and Lyme disease incidence in New Jersey (Jordan et al., 2007).

There are three primary reasons why the association between deer populations and black-legged ticks is often weak or variable. First, the black-legged tick is a host generalist in all three of its host-seeking life stages. Larvae and nymphs are known to feed on 41 species of mammals, 57 species of birds, and 14 species of lizards, while adults are known to feed on at least 27 species of mammals and 1 species of lizard. Second, when the population of a host species drops,

[1] The Committee notes evidence also supports the theory of deer being the definitive host. A mainland study in the same area as Monhegan documented a strong relationship of adult tick numbers and deer density (Rand et al, 2003), and studies by others (Wilson et al., 1988; Daniels et al 1993;) revealed similar tick reduction in the presence of alternative hosts for adult ticks.

ticks can aggregate on the remaining hosts. In the study reported by Deblinger et. al., (1993) the number of ticks per deer rose as the researchers reduced the deer population. The same phenomenon may occur with other (non-deer) hosts for adult ticks as well, but has yet to be studied. Third, there is no correlation between the abundance of larval ticks in one year and the abundance of nymphal ticks (Ostfeld et al., 2006). A disconnect is apparent between the factors affecting larval tick populations and those affecting nymph populations—and therefore the risk of Lyme disease. So even if deer abundance determines subsequent larval abundance, this might not be relevant to Lyme disease risk.

An important note is that all three life stages feed on a number of different hosts. Rather than making assumptions about which hosts are fed upon by black-legged ticks, scientists need to determine empirically the role that the different host species play in producing the nymph population. The size of the larval cohort does not predict the size of the nymphal cohort—the cohort that is responsible for transmission of the pathogen. The critical issues are how many of the larvae are able to find a host that will support successful feeding and how many hosts will infect the larval tick so that it becomes an infected nymph. Understanding the interactions between the various host species and the larval tick is critical.

A particular host species might encounter ticks at a typical rate based on its body size, the way it uses space, or some other factor that scientists do not yet understand. However, some ticks that encounter a host will be unable to feed because they will be groomed off and killed in the process—host permissiveness. The combination of encounter rates and permissiveness determines the number of larvae on a host—known as body burden—during the larval period. Furthermore, each host species may provide a different quality or quantity of blood to feeding larval ticks, affecting their rate of molting success and over the winter survival. Different host species also have different reservoir competence levels: that is, different probabilities that they will infect feeding larvae with a tick-borne pathogen.

Ostfeld and colleagues (Keesing et al., 2009) captured six types of birds and mammals—representing a range of taxonomic groups and body sizes—in August, when larval black-legged ticks were feeding. The animals were held in the laboratory for about 4 days, until all naturally acquired ticks had dropped off; the researchers then placed 100 larval ticks on each host, and followed their fate. There was significant variation in permissiveness among the host species. Approximately 50 percent of larval ticks that attempted a blood meal on white-footed mice succeeded, and dropped off in a replete state. Only 3.5 percent of larval ticks attempting a blood meal on an opossum succeeded, however, with the rest killed while trying to feed. Similarly, there was a significant variation in larval tick burden among species. When species were captured from the wild and the number of attached ticks determined, it was found that the average mouse hosts about 25 larval ticks, the average gray squirrel about 150 larval ticks, and the average opossum about 250 larval ticks. From these data, the encounter rate of larval ticks with hosts and the proportion of ticks that do not feed successfully as a result of low permissiveness can be estimated. The white-footed mouse grooms off and kills an average of 50 larval ticks per week, while gray squirrels groom off and kill approximately 843 larval ticks and opossums 5,686 larval ticks.

These species also vary in reservoir competence, with infected white-footed mice infecting approximately 90 percent of larval ticks that feed on them, and the other species, such as the white-tailed deer, raccoons, and opossums infecting very few larval ticks (see Figure 2-3). Although white-footed mice, and secondarily eastern chipmunks are ideal hosts for both feeding and infecting larval ticks with tick-borne pathogens, opossums, gray squirrels, and probably other hosts are not, which reduces the risk of human exposure to Lyme disease from these hosts. Thus, the composition of the host community for black-legged ticks in nature may determine risk for human Lyme disease.

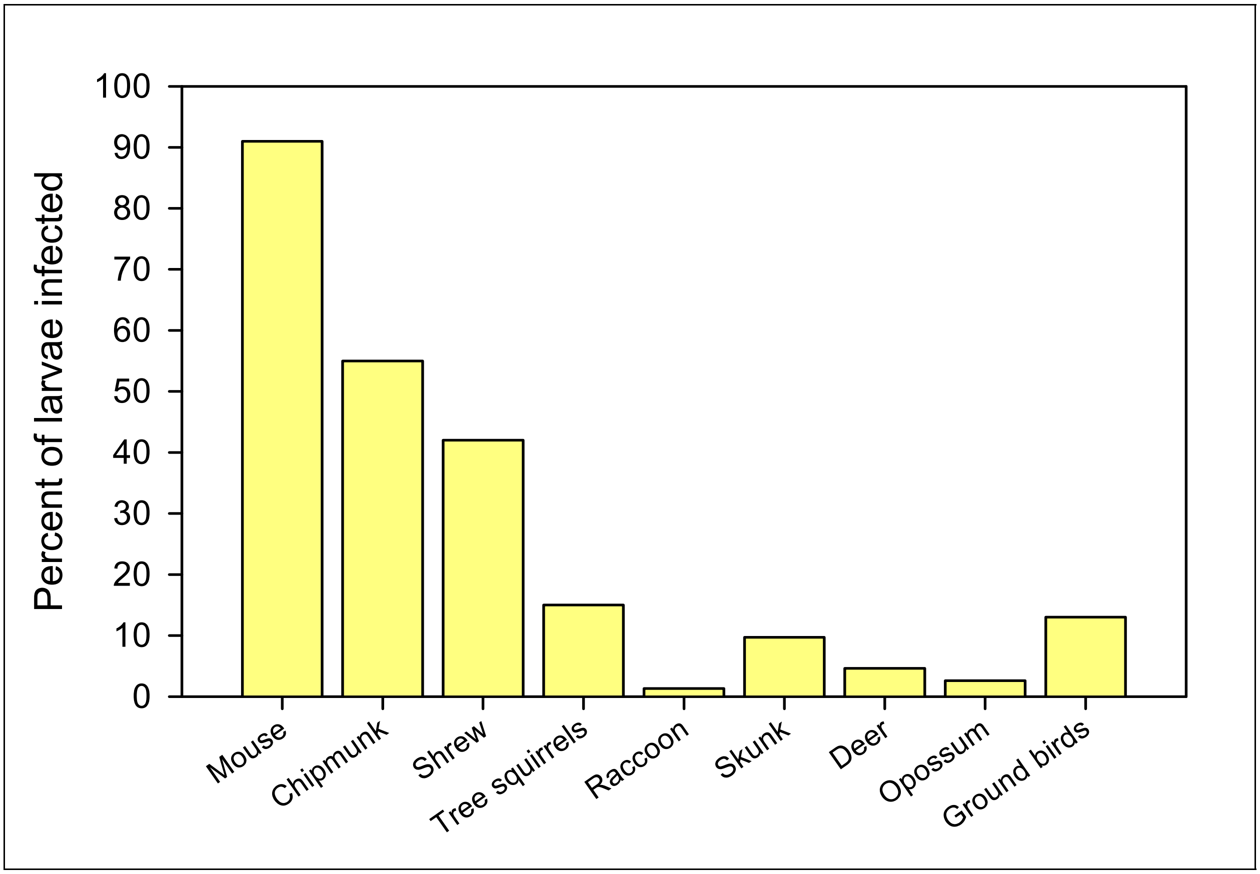

FIGURE 2-3 Reservoir competence of common *Ixodes* ticks in potential hosts in which high rates of larval infection reflect a greater risk of pathogen transmission during subsequent feeding cycles.

SOURCE: Updated from LoGiudice et al., 2003.

Vertebrate host populations are reduced when land is developed and habitats become fragmented. Primarily the large body animal species, which require large amounts of space to live, and the predatory species disappear. Small, omnivorous species, such as the white-footed mouse, tend to dominate small forest fragments. Based on the host competence data and host permissiveness studies, one likely outcome is an elevated risk of Lyme disease transmission in small forest fragments but not in larger forest fragments. In suburban Duchess County in southeastern New York, there was a significant negative correlation between the size of a forest fragment and the prevalence of Lyme disease infection in the nymphal tick population (Allan et al., 2003). In forest fragments smaller than about two or three hectares, the risk of human exposure to *Borrelia burgdorferi* rose by a factor of three or four. Public health officials could use this information to develop avoidance and intervention mechanisms by identifying landscapes that are likely to be the riskiest for transmission to humans.

Scientists do not yet know whether these findings apply to other tick-borne diseases such as human babesiosis, which emerged in 1966, and granulocytic anaplasmosis, which emerged in 1994. Hampering the research is the lack of a complete list of the natural reservoirs for the pathogens that cause those tick-borne diseases. However, initial work is beginning to test the role of various mammalian and avian hosts in infecting feeding larval ticks with the pathogens of these two emerging TBDs.

Knowledge Gaps and Research Opportunities

Ostfeld identified a number of key questions remain for future study:

- *Which factors other than the size of forest fragments predict the abundance of ticks and the prevalence of Lyme disease?* Some studies show that certain types of edges between forest and non-forest habitats influence the risk of Lyme disease transmission. Other studies show that the types of matrixes surrounding forest patches are important. The degree of isolation of these fragments can also influence the vertebrate host community. Understanding these factors and their impact will require much more research.
- *Do Lyme disease, anaplasmosis, and babesiosis share common risk factors?* If different hosts play different roles in infecting ticks with the pathogens that cause these diseases, that would suggest that the environmental determinants of risk of Lyme disease versus other tick-borne diseases are decoupled.
- *Which animal hosts of Ixodes scapularis ticks are of critical importance in determining the tick population density?*
- *Which local and landscape features affect human use of forests and other habitats, and hence their contact with ticks?* Although the density of infected nymphs in small forest fragments might be high, this finding may not be tremendously important for Lyme disease if people prefer to use more extensive forests for recreation. The decoupling of entomological risk and human behavior will mean that different educational and environmental interventions are needed to reduce risk.

DISCUSSION

During the discussion, the participants and Ostfeld focused on the roles of various hosts, ticks, and habitats in the transmission of *B. burgdorferi* to humans and how this knowledge can be used to predict the occurrence of new areas for tick populations and to develop public health strategies aimed at reducing transmission of the disease.

The Role of Migratory Birds in Tick Distribution

Several studies (Smith et al., 1996; Klich et al., 1996) have shown the nymphal tick burdens on migratory birds in the northeastern and midwestern United States and in Canada, where researchers have hypothesized that migratory birds are responsible for moving significant numbers of ticks long distances into areas where populations might not otherwise occur or for increasing the number of ticks in an already populated area. Ostfeld noted that this is another emerging frontier for research. Some evidence suggests that the ticks that are moved around by migratory birds tend to have low infection prevalence because, with a few exceptions, migratory birds are not highly competent reservoirs. However, the research is not complete and the data is limited.

Reservoir–Competent Hosts

The need for ongoing research to identify why some host species have low or zero reservoir competence was suggested by some participants who cited the fact that lizards are not competent hosts. Ostfeld noted that the reason for low reservoir competence can vary by species. In the case of lizards, circulating proteins prevent infection. In other cases, such as opossums or gray squirrels, it is unknown whether low reservoir competence is a function of that complement system, which is innate or of induced immunity, including antibody production.

Environmental Factors Affecting Tick Populations

One participant questioned the relationship between the population size of larval ticks and the opportunities for feeding on hosts. Ostfeld noted that researchers have found that acorn abundance is a reliable predictor of infected nymphal ticks 2 years later. In studies in New York, increased acorn production both attracts white-tailed deer and boosts populations of white-footed mice, with a subsequent increase in the abundance of larval ticks (Ostfeld et al., 1996; Jones et al., 1998).

Transovarial Transmission

Studies in the late 1980s assessed questing larval ticks for prevalence of infection with spirochetes. The rate of infected larval ticks was approximately 1 percent, but the techniques used were not highly specific to *B. burgdorferi* (Piesman et al., 1986). One participant questioned whether the larvae's role in transmitting disease to human has been underrecognized. Ostfeld noted that other spirochetes are known to have a more efficient transovarial transmission and the 1 percent rate noted in these studies may be these other spirochetes. The evidence of the lack of transovarial transmission comes from experimental studies that were done with adult ticks feeding on hosts known to be infected with *B. burgdorferi* spirochetes. The larval ticks that hatched from the eggs of infected ticks were not infected.

Land Use and Public Health Strategy

The relationship of tick and host habitat to the transmission of disease to humans was an area of considerable interest in which participants and Ostfeld discussed land-use strategies and the potential influence on public health. One participant asked whether there is an inherent geographic or landscape scale limit on the spread of Lyme disease. Ostfeld noted that it is possible to sample various areas to estimate tick abundance and to use Landsat imagery to examine the correlates. With these estimates, scientists can make models of how the ticks will spread. The problem is that the risk maps are created on a dynamic system, which results in underestimating the suite of potentially favorable conditions under which ticks can occur. As a result, ticks may inhabit areas that the risk maps do not indicate as favorable

The research presented suggests an opportunity for engaging with regional planners in terms of forest fragmentation, observed one participant. Ostfeld concurred that engaging various county- and city-level government agencies is an area for future collaboration. The challenge lies in translating ecological observations into actual policy at the local, regional, and county levels, and more discussion is needed to determine how to integrate these observations into zoning and planning.

Other participants focused on specific strategies such as placing signage in high-risk areas or using pesticides. Ostfeld agreed that both of these strategies had promise. For example, the Tick Task Force in Duchess County has placed signs at trail heads and in public parks. The signs not only point out that the danger of exposure to pathogen-bearing ticks is high, but also offer advice on how to reduce risk through personal protection measures. Targeted pesticide usage is an area of further discussion, Ostfeld noted. This strategy would benefit public health by targeting application in areas where both the incidence of infected ticks and human use are high—such as school fields—while reducing the collateral damage from overuse of pesticides.