2nd Report

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Tick-Borne Disease Working Group

2020 Report to Congress

Information and opinions in this report do not necessarily reflect the opinions of each member of the Working Group, the U.S. Department of Health and Human Services, or any other component of the Federal government.

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Executive Summary

The Tick-Borne Disease Working Group 2020 Report to Congress addresses continuing key gaps in the diagnosis and treatment of Lyme disease and adds additional focus on other tick-borne diseases and conditions in the United States. These include life-threatening Rocky Mountain spotted fever, human monocytotropic ehrlichiosis, human granulocytotropic anaplasmosis, babesiosis, emerging tick-borne viruses and other pathogens, as well as Alpha-gal Syndrome, the serious allergic condition associated with lone star ticks.

Seventy-seven percent of vector-borne diseases in the United States are transmitted by ticks, and their incidence has risen dramatically in recent decades (Petersen, Beard, & Visser, 2019). There are currently seven reportable tick-borne diseases (Rosenberg et al., 2018). Additionally, 11 novel tick-borne pathogens have been identified in the United States since the early 1980s (R. J. Eisen & Paddock, 2020). These infections are under-recognized and under-reported. In the case of Lyme disease, the actual number of annual cases has been estimated at 8 to 12 times higher than the number of reported cases (Hinckley et al., 2014; Nelson et al., 2015). Human monocytotropic ehrlichiosis is under-reported by an estimated tenfold to one hundredfold (Olano, Masters, Hogrefe, & Walker, 2003), and human granulocytotropic ehrlichiosis by an estimated elevenfold (J. S. Bakken & Dumler, 2015; J. S. Bakken et al., 1996; CDC Division of Health Informatics and Surveillance, 2018; IJdo et al., 2000).

In the shadow of the COVID-19 pandemic, it is likely that many people seeking the solace and safety of outdoor activities are having increased exposure to tick-transmitted diseases. The geographic range of both blacklegged ticks and lone star ticks has expanded greatly over the last 20 years. Additionally, the numbers of pathogens that are now known to be carried by these ticks—and the conditions associated with ticks bites, such as Alpha-gal Syndrome—have increased significantly (Table 1, p. 4). Consequently, more and more people are suffering from tick-associated illnesses each year.

This report addresses not only tick-borne diseases, but also the biology, ecology, and control of the ticks that transmit disease. Included is a recommendation to adopt a One Health interdisciplinary, collaborative approach in health care for humans, animals, and the environment leading to integrated tick management to prevent transmission of tick-borne diseases.

Also underscored is the critical need for improved diagnostics, clinician training and education, and an enhanced surveillance process. These areas are interlinked in that a clinician must be aware of the disease in order to consider it in the differential diagnosis; have accurate and effective diagnostic tools combined with a complete understanding of how to administer and interpret them; and be able to report positive results within a standardized surveillance system that is not overly taxing to clinicians.

The lack of clinician or provider awareness and knowledge of tick-borne diseases, especially life-threatening treatable diseases such as Rocky Mountain spotted fever, human monocytotropic ehrlichiosis, and human granulocytotropic anaplasmosis, prompted several recommendations for increased medical education at all career levels for all tick-borne diseases. Clinician training and education modules should include the clinical manifestations, interpretation of diagnostic tests, and appropriate treatment. Indeed, the emerging tick-borne diseases need acquisition of fuller knowledge of the clinical spectrum of illness.

Diseases are not reported if they are undiagnosed. The lack of generally available laboratory testing methods to provide diagnoses during the acute stage of illness when treatment is most effective needs to be addressed by funding innovative approaches, including the development of point-of-care diagnostic tests.

Epidemiology currently relies on surveillance provided by passive reporting, capturing only a fraction of tick-borne disease cases. Moreover, the reporting process, particularly for Lyme disease, is complex and burdensome, which contributes to the issue of under-reporting. Prospective studies of undifferentiated acute febrile illness are required to determine the burden of disease. Such studies in different geographic regions would enhance understanding of disease incidence, or new cases each year. In addition, a standardized surveillance process that allows for direct laboratory reporting of positive cases would allow for the collection of accurate, up-to-date incidence data for all tick-borne diseases.

Alleviating and preventing patient suffering remains at the forefront of the recommendations by the Tick-Borne Disease Working Group (hereafter, "Working Group"). Particularly for Alpha-gal Syndrome and Lyme disease, there is a critical need for studies to elucidate their pathogenesis (or mechanism of disease) and to search for effective therapeutic or preventive targets. Today, we recognize that acute tick-borne diseases, such as Rocky Mountain spotted fever and ehrlichiosis, are managed with antibiotic therapy to prevent patient debilitation, disability, and death. Similarly, when treating Lyme disease, clinicians administer antibiotic treatment, often supported by clinical practice and evidence-based guidelines, as they seek the recovery of patients. Yet because not all patients recover and some may suffer from persistent symptoms or chronic disease, more research is needed to guide the approach to acute disease and to prevent death. Specifically, research is needed to understand whether or not persistent infection or bacterial products play a role in the overwhelming problem of prolonged symptoms associated with Lyme disease. In addition, investigation of antibiotic regimens and other therapeutic approaches, including novel and supplemental treatments, is critical to addressing patient needs.

In addition to the evaluation of available research and stakeholder input, this report is informed by responses to a Federal inventory survey supplied by Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, U.S. Department of Defense, National Institutes of Health, U.S. Department of Veterans Affairs, and U.S. Food and Drug Administration. The results revealed impressively extensive and important Federal activities related to tick-borne diseases and stimulated recommendations by the Working Group to those agencies.

Also captured in this report are the concerns outlined by members of the public, who continuously provided input throughout the report development process and whose concerns were considered by all Working Group members, as well as a subcommittee devoted entirely to cataloguing and processing their comments.

The recommendations in this report are equally important and often interwoven, with the success of one dependent on the implementation of another. The Working Group thanks Congress and the HHS Secretary for soliciting this information and respectfully requests that its recommendations be approved and funded with the goal of dramatically improving patient outcomes and reducing the societal burden of tick-borne diseases in our country.

The Working Group acknowledges that there remains room for continued assessment, action, and hope to address the Federal government's response to all tick-borne diseases. Congress and the HHS Secretary will define the future path towards a common goal of preventing Lyme disease and other tick-borne diseases and conditions.

Chapter 1
Background

Diseases transmitted by ticks are a serious and growing public health concern. Lyme disease is the most common tick-borne disease with an estimated 300,000 new cases diagnosed in the United States each year (Hinckley et al., 2014; Nelson et al., 2015). Several other tick-borne diseases and conditions also pose a significant threat, in part because they are less widely recognized and often go undiagnosed, resulting in serious health consequences, even death. Rocky Mountain spotted fever, first recognized in the early 20th century, can be fatal if not treated within the first few days following transmission. Other tick-borne diseases and conditions have emerged in recent decades including Powassan virus (1958), human ehrlichiosis (1987), human anaplasmosis (1990), and Alpha-gal Syndrome (2009), a condition that results in a potentially life-threatening allergy to products derived from mammals. Table 1 lists tick-borne diseases and conditions currently recognized in the United States.

Table 1: Tick-Borne Diseases and Conditions Currently Recognized in the United States

Pathogen type	Disease (or condition)	Pathogen (U.S.)	Tick vector (U.S.)
Bacteria	Lyme disease (acute, persistent)	*Borrelia burgdorferi* *Borrelia mayonii*[1]	Blacklegged tick Western blacklegged tick
	Borrelia miyamotoi infection	*Borrelia miyamotoi*[2]	Blacklegged tick
	Tick-borne relapsing fever	*Borrelia hermsii, B. turicata, B. parkeri* and others	Soft ticks (Ornithodoros species)

Pathogen type	Disease (or condition)	Pathogen (U.S.)	Tick vector (U.S.)
Bacteria (continued)	Anaplasmosis	*Anaplasma phagocytophilum*	Blacklegged tick, western blacklegged tick
	Ehrlichiosis	*Ehrlichia chaffeensis*	Lone star tick
		Ehrlichia ewingii	Lone star tick
		Ehrlichia muris eauclairensis	Blacklegged tick
	Tularemia	*Francisella tularensis*	American dog tick, Rocky Mountain wood tick, lone star tick
	Rocky Mountain spotted fever	*Rickettsia rickettsii*	American dog tick, brown dog tick, Rocky Mountain wood tick
	Other spotted fever	*Rickettsia parkeri*	Gulf Coast tick
	Pacific coast tick fever	*Rickettsia philipii*	Pacific Coast tick
Virus	Powassan disease	Powassan virus	Blacklegged tick, groundhog tick
	Colorado tick fever	Colorado tick fever virus	Rocky Mountain wood tick
	Bourbon virus	Bourbon virus	Lone star tick (putative)
	Heartland virus	Heartland virus	Lone star tick
Parasite	Babesiosis	*Babesia microti, B. duncani, B. divergens,* MO-1	Blacklegged tick
Unknown	Southern tick-associated rash illness	Unknown	Lone star tick

Pathogen type	Disease (or condition*)	Pathogen (U.S.)	Tick vector (U.S.)
None	*Alpha-gal syndrome	None	Associated with Lone star ticks and chiggers
	Tick paralysis	None	American dog tick, Rocky Mountain wood tick

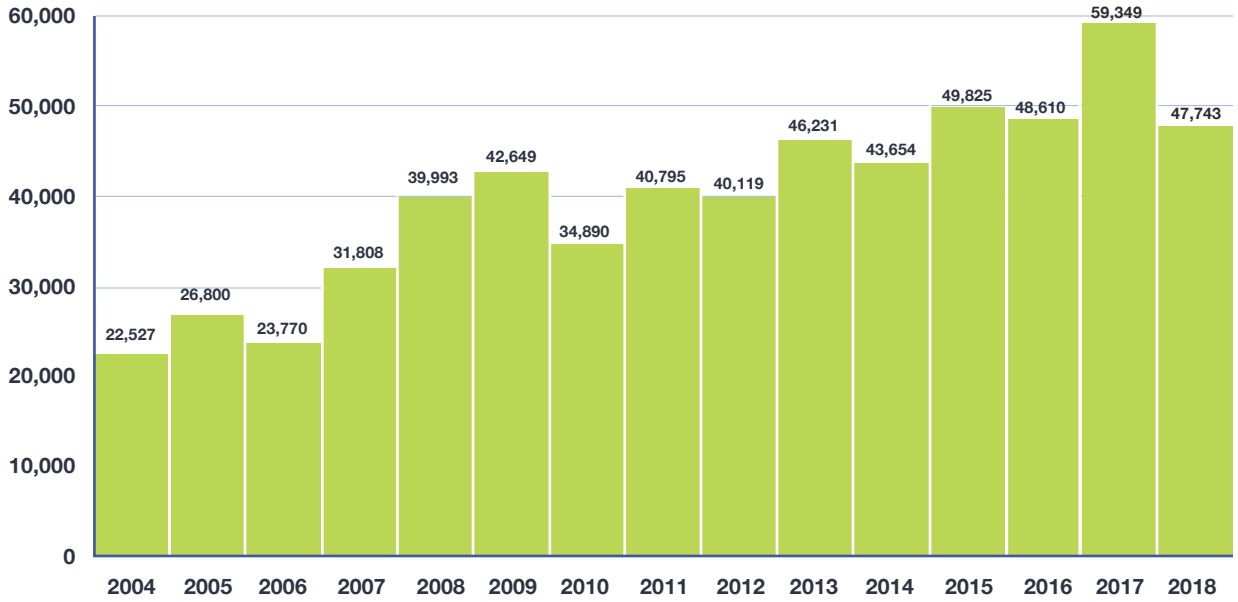
[1] Borrelia mayonii *is a recently discovered pathogen that causes Lyme disease. It has not to date been associated with the western blacklegged tick.*

[2] Borrelia miyamotoi *is a recently discovered pathogen that causes a relapsing fever and is genetically more similar to the relapsing fever Borrelia species.*

Source: Derived from *Table 1. Tickborne Diseases of the United States*, NIH Strategic Plan for Tickborne Disease Research, October 9, 2019. Retrieved from https://www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf

Reported cases of all tick-borne diseases and conditions have been increasing steadily. Between 2004 and 2017, case reports to the Centers for Disease Control and Prevention (CDC) nearly tripled (Figure 1); yet the actual incidence of human transmission remains unknown. Because tick-borne diseases and conditions are severely under-reported, their numbers are likely higher than surveillance activities currently capture. Moreover, tick populations continue to grow, and infected ticks expand geographically, intensifying the risk to human health. Consequently, each year more people are living in areas of risk for exposure to the bites of infected ticks.

Figure 1: Annual Reported Cases of Tick-Borne Diseases in the United States



Source: Centers for Disease Control and Prevention (2019). *Total Reported Cases of Tickborne Disease, 2004–2018*. Retrieved from https://www.cdc.gov/ticks/data-summary/index.html

Tick-borne diseases and conditions are often difficult to diagnose. Their symptoms can be easily confused with those of other illnesses and allergies (in the case of Alpha-gal Syndrome). In addition, current diagnostic methods are often inadequate during the acute stage of illness when crucial therapeutic decisions are required, and some have other important limitations. These constraints, coupled with scientific uncertainty and gaps in knowledge and education about how to use available tests, frequently result in misdiagnosed and undiagnosed tick-borne diseases. Complications arise when patients have simultaneous infections of two or more tick-borne pathogens, a condition called co-infection. This can result from one tick transmitting two or more pathogens to a single human host or from the host's exposure to the bites of more than one infectious tick. Moreover, many patients experience persistent symptoms, recurring symptoms, and/or long-term damage (sequelae) after treatment. Persistent illness associated with Lyme disease is poorly understood and often results in significant deterioration in the quality of life of patients and their caregivers.

The expense of diagnosing and treating tick-borne diseases and conditions, paired with loss of productivity, represent a significant economic burden for individual patients, their families, and the American public. For Lyme disease alone, direct medical costs could reach 1.3 billion dollars each year, and these costs increase significantly when therapy fails to return patients to baseline health (Adrion, Aucott, Lemke, & Weiner, 2015). The bulk of Lyme disease-related costs are due to indirect medical costs, nonmedical costs, and lost productivity, all of which increase with longstanding disease

(Zhang et al., 2006). The recommendations in this report are intended to alleviate these burdens by preventing tick-borne disease transmission and facilitating access for both clinicians and patients to vital information and tools they need for prompt, effective diagnosis and treatment.

Congressional Action

In December 2016, Congress passed the *21st Century Cures Act* (Appendix D), designed to promote new healthcare innovations for addressing an array of public health issues. Section 2062 of the legislation pertains to advancing research on tick-borne diseases. The Act requires the U.S. Secretary of Health and Human Services (HHS) to establish a working group to review current research efforts, identify priorities and gaps related to tick-borne diseases, and provide a report of its findings to Congress and the HHS Secretary every two years (in 2018, 2020, and 2022). In response, the HHS Secretary formed the Tick-Borne Disease Working Group (hereafter "Working Group").

The Tick-Borne Disease Working Group

The Working Group comprises diverse stakeholders, including Federal and public members representing various perspectives and areas of expertise (Appendix A). The Working Group includes 14 individuals appointed by the HHS Secretary. Seven are public voting members and seven are Federal voting members. Public members include scientists, clinical researchers, physicians, a patient (recovered), and a patient advocate. Federal appointees to the Working Group represent Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, National Institutes of Health, Office of the Assistant Secretary for Health, U.S. Food and Drug Administration, U.S. Department of Defense, and U.S. Department of Agriculture

A Charter approved by the HHS Secretary governs the Working Group's structure and activities (Appendix E). In compliance with *Federal Advisory Committee Act* (FACA) requirements, Working Group meetings are open to the public, and meeting materials and summaries are posted publicly. The Working Group Co-Chairs, appointed by the HHS Secretary, conduct Working Group meetings.

Second Report: Focus and Structure

This report, the second of three, does not repeat but instead expands upon the recommendations put forth by the Tick-Borne Disease Working Group in its 2018 Report to Congress, which are still important today. Those recommendations prompted the Federal government to develop several initiatives that will directly benefit both tick-borne disease patients and providers. Specifically:

- The National Institutes of Health released its Strategic Plan for Tickborne Disease Research, which aims to build on current NIH efforts to better understand tick-borne diseases and develop "tools and strategies to prevent, diagnose, and treat" them (National Institutes of Health, 2019).

- The Centers for Disease Control and Prevention initiated a national tick surveillance program with the goal of coordinating, funding, and standardizing tick surveillance activities at the state, municipal, and territory level (Beard, personal communication, 2020; CDC, 2020h).
- Congress passed the Kay Hagan Tick Act "to provide assistance to combat the escalating burden of Lyme disease and other tick and vector-borne diseases and disorders" (S.1657, 116th Congress, 2019).

The Working Group fully supports these initiatives and wrote this report with the intention of building and expanding upon them.

The content in this report is the result of in-depth analysis of the available science, including real-world evidence related to ticks, pathogens, and human disease, and the assessment of the inventory provided by Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, National Institutes of Health, U.S. Department of Defense, U.S. Department of Veterans Affairs, and U.S. Food and Drug Administration. The report describes a potential path forward for addressing the spread, diagnosis, and treatment of tick-borne diseases. It is structured according to the priority areas identified by the Working Group:

- Tick Biology, Ecology, and Control
- Clinical Manifestations, Diagnosis, and Diagnostics
- Causes, Pathogenesis, and Pathophysiology
- Treatment
- Clinician and Public Education, Patient Access to Care
- Epidemiology and Surveillance
- Federal Inventory
- Public Input
- Looking Forward

Chapters 3 through 8 present a background overview, challenges and obstacles associated with each topic, scientific and clinical research related to tick-borne diseases, and current gaps in Federal research and activities. Sections conclude with recommendations to the U.S. Congress and the HHS Secretary for addressing tick-borne diseases.

Chapter 2
Methods of the Working Group

The Tick-Borne Disease Working Group used information from three topic development briefs, eight subcommittee reports, the Federal inventory of activities, public comments, and the latest available science to develop the Tick-Borne Disease Working Group 2020 Report to Congress. This section describes the subcommittees involved in this work, the Federal inventory, and the process for receiving and reviewing public comments.

Topic Development Briefs

In June 2019, the Working Group identified three questions for literature reviews. *Ad hoc* subcommittees were formed to refine the questions and help develop literature search criteria for the following topics.

- Increases in Tick-Borne Diseases
- Diagnostic Tests for Tick-Borne Diseases
- Persistent Symptoms of Lyme Disease

The briefs are available at https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/topic-development-briefs/index.html.

Subcommittees

Also in June 2019, the Working Group formed eight subcommittees composed of members with relevant expertise and experience to gather information, data, and research that would enable the Working Group to thoroughly examine several aspects of diagnosing, treating, and preventing tick-borne diseases and conditions. Each Working Group member volunteered to co-chair at least one of the following subcommittees, ensuring that each subcommittee included one Federal member and at least one public member from the Working Group.

- Alpha-gal Syndrome (AGS)
- Babesiosis and Tick-Borne Pathogens
- Clinical Aspects of Lyme Disease
- Ehrlichiosis and Anaplasmosis

- Pathogenesis and Pathophysiology of Lyme Disease
- Rickettsiosis
- Tick Biology, Ecology, and Control
- Training, Education, Access to Care, and Reimbursement

Subcommittee membership encompassed a broad range of perspectives, with at least one patient or patient advocate on each subcommittee. Subcommittee size ranged from seven to 16 individuals.

The Working Group Co-Chairs and the Designated Federal Officer tracked progress of all subcommittees through weekly status update meetings.

Over a six-month period, weekly or biweekly subcommittee meetings offered opportunities for open dialogue and presentations from subject matter experts. Each subcommittee identified several priorities, broke up into writing groups, and developed a report to the Working Group that described current efforts, gaps in research, and potential actions to address each priority. In drafting their reports, the subcommittees compiled information from expert, advocate, and patient presentations; collective subcommittee member knowledge; and literature reviews. In finalizing their reports, subcommittee members voted on the potential actions and included minority opinions expressed by subcommittee members. During the Working Group Public Meeting 11 (January 28-29, 2020), subcommittee co-chairs presented their findings to the Working Group.

It is important to note that the subcommittees were established to conduct preparatory work for the Working Group to consider, and their work process differed from the process of the Working Group. For example, the subcommittees were not required to follow the same FACA requirements (41 C.F.R. § 102–3.35; 41 C.F.R. at § 102–3.160(a)). Through its work process, each subcommittee drafted a report that synthesized relevant science, addressed current practice issues and patient needs, and identified potential actions for the Working Group to consider. Each subcommittee provided a slide presentation highlighting the report's background, methods, potential actions, and rationale. The Working Group then discussed the potential actions, modified them (if necessary), and voted to approve, modify, or reject them as recommendations to be included in the Tick-Borne Disease Working Group 2020 Report to Congress. All subcommittee reports are available at https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/index.html.

In addition to the eight subcommittees described previously, the Working Group formed two additional subcommittees, composed of Working Group members, to process and synthesize input received from the Federal Inventory survey and from members of the public. Their activities are described below.

Federal Inventory

To gather information on Federal activities that address tick-borne diseases, the Working Group developed a Federal project inventory survey (Appendix F), which was distributed to Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), National

Institutes of Health (NIH), U.S. Department of Defense (DoD), U.S. Department of Veterans Affairs (VA), U.S. Department of Agriculture (USDA), and U.S. Food and Drug Administration (FDA). The Working Group received inventories from all agencies. Six agencies (CDC, NIH, FDA, CMS, DoD, and VA) had participated in the 2018 Federal project inventory survey, and they provided updated information on activities that took place after the Tick-Borne Disease Working Group 2018 Report to Congress was submitted. USDA did not participate in the 2018 inventory survey and, therefore, provided a complete accounting of all related activities.

To process the inventories received, the Working Group formed a Federal Inventory subcommittee of three members to oversee the process and synthesize the information provided. The results of their work are detailed in Chapter 9. The complete inventory survey results can be obtained by any individual who submits a request through the Tick-Borne Disease Working Group emailbox (tickbornedisease@hhs.gov).

Public Input

In compliance with FACA requirements, the Working Group provided opportunities for public comment through the following channels:

- Verbal comments given at Working Group public meetings – At all Working Group meetings, time was allocated for the public to provide comments in person or over the phone. Each commenter was limited to three minutes to accommodate as many speakers as possible.
- Written comments submitted prior to the Working Group public meetings – Prior to the Working Group meetings, the public was invited to send their written comments to the Working Group. This method provided an opportunity for those who could not participate in the meetings to have their public comments reviewed and considered in advance.
- Email comments – In addition, the public had an opportunity to email their comments to the Working Group (tickbornedisease@ hhs.gov) at any time, on any day. Emails received before November 1, 2020 were reviewed and considered in this report. Those received after October 31, 2020 will be considered for the third Working Group report.

The entire Working Group received all public comments in Word documents. To process the comments, the Working Group formed a Public Comments subcommittee of three members who read all comments and synthesized key themes by month, which they reported at public meetings in the slide presentation. They also sorted comments by topic area, which they organized into spreadsheets and provided to the other Working Group subcommittees to consider integrating into their source materials. The results of their work are summarized in Chapter 10. In addition, comments received for all meetings can be viewed in each meeting tab on the Tick-Borne Disease Working Group website (https://www.hhs.gov/ash/advisory-committees/tickbornedisease/meetings/index.html).

Minority Responses

Some of the content in this report had opposing viewpoints. These are expressed as minority responses within the relevant chapters. Minority responses reflect the views of the individual authors and do not necessarily reflect the views of the Working Group or the U.S. Department of Health and Human Services.

Chapter 3

Tick Biology, Ecology, and Control

Recommendations at a Glance: Tick Biology, Ecology, and Control

Recommendation 3.1: Implement multi-agency, ecologically-based One Health efforts on tick-borne diseases promoting research and enhanced vector surveillance to identify and validate integrated tick management in keystone wildlife hosts, particularly white-tailed deer, and the sustainable management of their populations.

Recommendation 3.2: Minimize the public health threat of Lyme disease and other tick-borne diseases through special funding for integrated tick management, disruption of tick biological processes contributing to pathogen transmission, and the support of public-private partnerships to develop and promote area-wide tick control strategies.

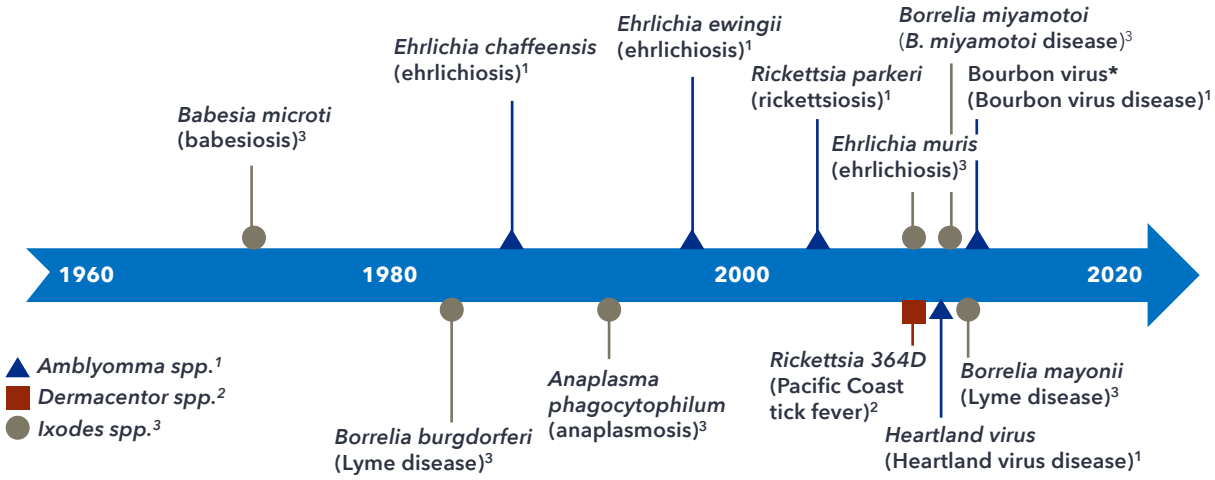
Recommendation 3.3: Provide funding to support CDC-directed expanded tick surveillance and promoting the development and implementation of best practices for integrated tick management capturing human tick bite events, and streamlining education, training, and coordination amongst relevant Federal, state, and local agencies.

Background

Tick-borne infectious diseases are complex systems defined as zoonotic because the disease-causing agent, or pathogen, is transmitted from wildlife or a domestic animal to a susceptible human through the bite of an infected tick (Brooks & Boeger, 2019; L. Eisen, 2020; Wikel, 2018b). The increasing incidence of tick-borne diseases and conditions threatens public health in the United States and other parts of the world (R. J. Eisen, Kugeler, Eisen, Beard, & Paddock, 2017; Perronne, 2014). Reported cases of tick-borne diseases recently more than doubled in the United States and represent 77 percent of

all vector-borne disease reports (Petersen et al., 2019). Shifts in the ecology and adaptive biology of tick disease vectors drive the spread of tick-borne diseases killing humans (Sonenshine, 2018; Wikel, 2018b). Currently, the Centers for Disease Control and Prevention (CDC) recognize 18 tick-borne pathogens in the United States. Moreover, researchers and clinicians continue to discover emerging pathogens (Figure 2) and new medical conditions associated with tick bites (Madison-Antenucci, Kramer, Gebhardt, & Kauffman, 2020; Sanchez-Vicente, Tagliafierro, Coleman, Benach, & Tokarz, 2019). This includes Alpha-gal Syndrome, a potentially life-threatening allergy to red meat and other mammal-derived products and ingredients.

Figure 2: Increasing Number of Tick-borne Pathogens, 1960-2018



***** Putative vector

• Year represents when tickborne pathogens was recognized as cause of human disease.

Adapted from: Eisen and Paddock, 2020. *Journal of Medical Entomology*; doi: 10.1093/jme/tjaa087

The number of reportable tick-borne pathogens has nearly doubled since the turn of the twentieth century. Between 1900 and 1960, researchers discovered seven tick-borne pathogens known to cause human disease, including *Rickettsia rickettsii* (Rocky Mountain spotted fever); *Francisella tularensis* (tularemia); *Borrelia turicata*, *Borrelia hermsii*, and *Borrelia parkeri* (tick-borne relapsing fever); Colorado tick fever virus (Colorado tick fever disease); and Powassan virus (Powassan encephalitis). Since 1960, 11 more pathogens have been classified, mainly in the past two decades.

Factors contributing to the increased risk of tick-borne diseases include climate and environmental change, host and vector population increases, range expansion, human use of tick habitats, and introduction of foreign ticks (Tick-Borne Disease Working Group *ad hoc* Subcommittee, 2019). An enhanced understanding of the reasons for the rising incidence of tick-borne diseases will help scientists and healthcare professionals develop strategies to lower the risk for disease transmission.

Additional activities and research in the following areas will ultimately provide practical approaches to reduce the risk of tick-borne diseases and conditions:

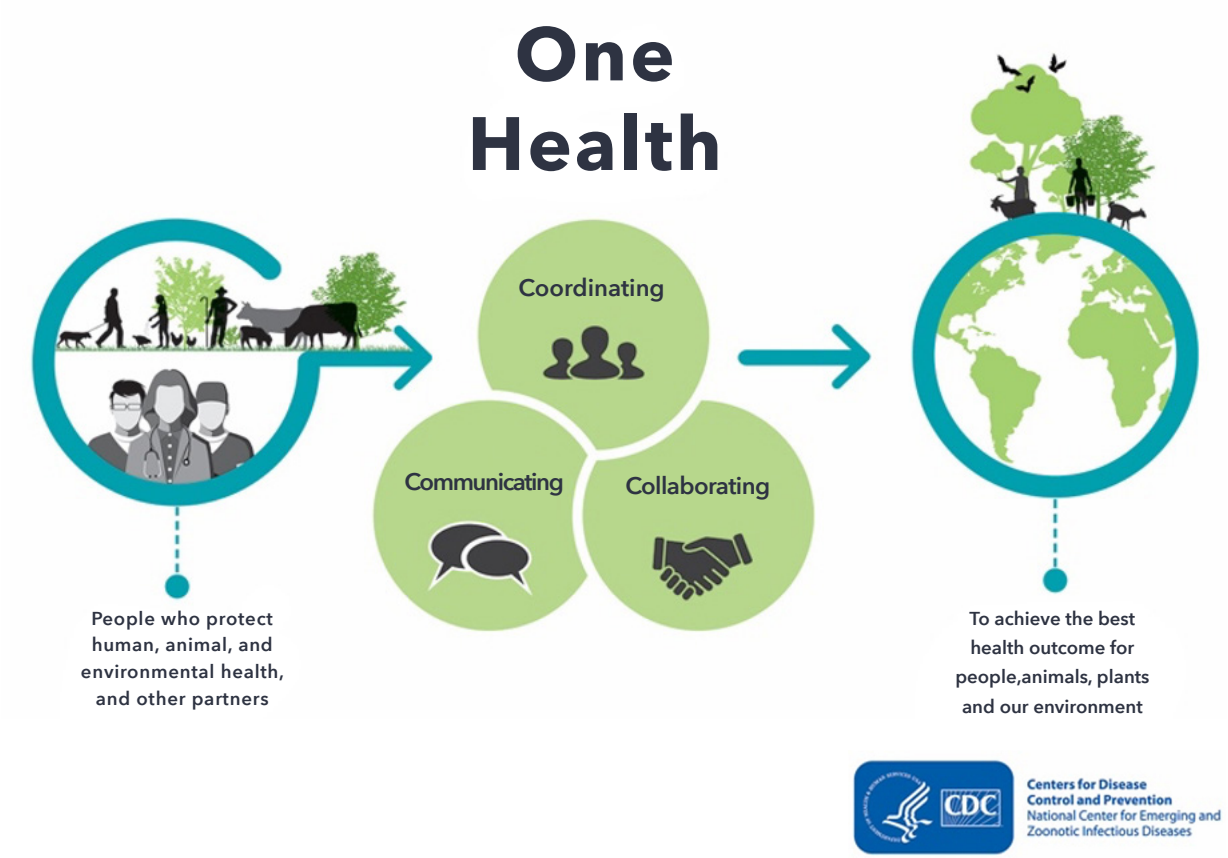
- Identification and understanding of the environmental and human behavioral determinants (climate and habitat variability as well as human landscape use patterns) driving tick spread and increases in tick populations and human-tick encounters.
- Improved communication and sharing of best practices between tick/pest management experts, human and animal health experts, and Federal agencies.
- Improved surveillance for established and newly introduced tick vectors.
- Development and adoption of effective management and control strategies for established and emerging tick species.
- Identification and removal of barriers to effective management and control strategies for established and emerging tick species.

The Tick-Borne Disease Working Group identified three focus areas that will advance these activities.

Adopt a One Health Approach to Employ Integrated Tick Management and Exploit Ecological Weaknesses of Tick-borne Disease Systems

One Health is a strategy that promotes interdisciplinary collaborations in health care for humans, animals, and the environment (American Public Health Association, 2017). It is intended to advance health care by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care (Figure 3). In this context, integrated tick management is practiced at the local level. To accomplish this, best practice guidance must be established, and more research is required to demonstrate the effectiveness of combining technologies for area-wide deployment (Clow, Leighton, Pearl, & Jardine, 2019; Stafford, Williams, & Molaei, 2017). This highlights the need for Federal support of public-private partnerships to help develop, validate, and promote tick control strategies, such as the CDC-led effort that resulted in the discovery of nootkatone, which was registered by the Environmental Protection Agency to repel and kill ticks (CDC, 2020d).

Figure 3: One Health Approach



Source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases. Retrieved from https://www.cdc.gov/onehealth/images/multimedia/one-health-definition-graphic-with-bats.jpg

The One Health approach promotes communication, collaboration, and coordination between multiple stakeholders within different domains in order to solve complex problems in public health. Investment in public-private partnerships that employ this approach can help tackle tick control at the local level, alleviate the burden on individuals, employees, and homeowners, and reduce their exposure to ticks and tick-borne diseases.

Taking the One Health approach will also facilitate the discovery and successful implementation of area-wide integrated tick management. Just as the practice of integrated tick management leverages ecological interactions to reduce the incidence of ticks, the One Health approach can be used to foster relationships between Federal, state, and local agencies, universities, private companies, and centers of excellence to minimize the risk of tick-borne diseases and conditions.

Identify and Validate Integrated Tick Management Strategies

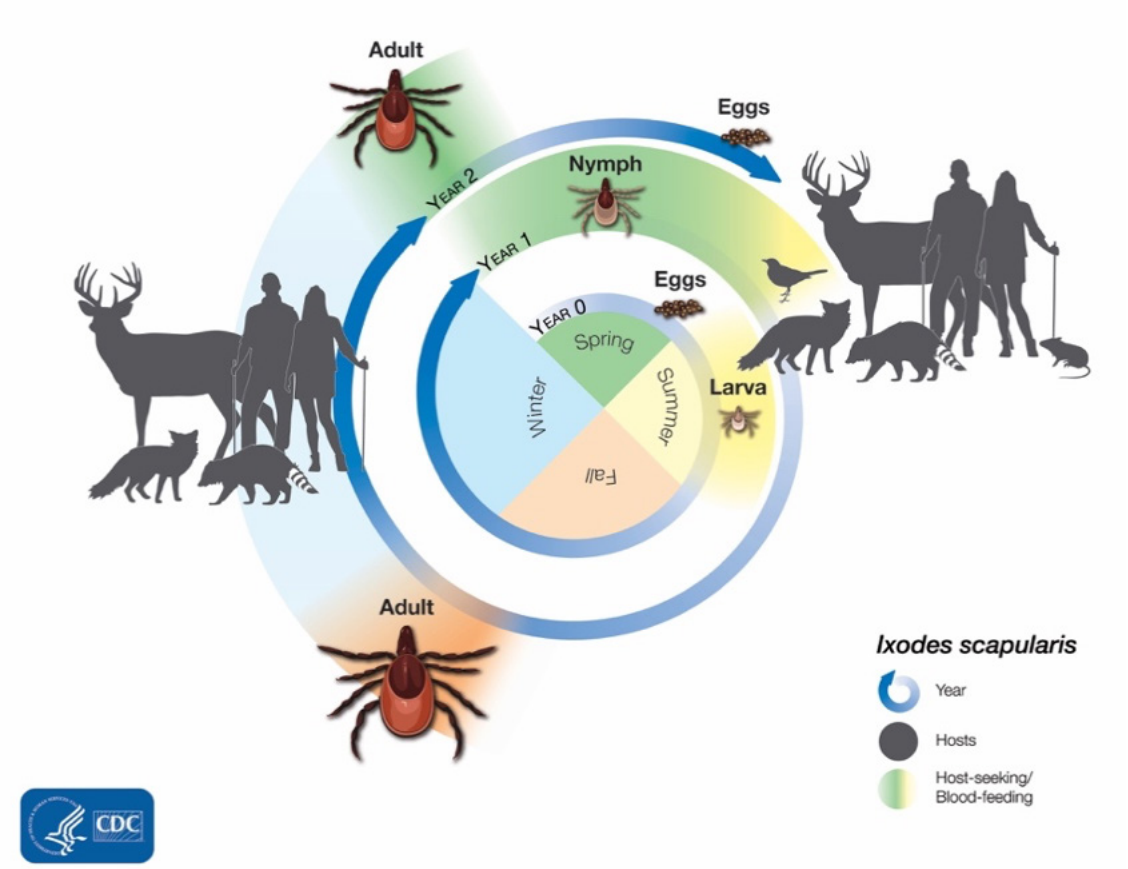
In recent decades, the burden of controlling ticks has fallen largely on individuals, employees, and homeowners, who must take it upon themselves to mitigate their exposure to ticks. However, they are often unable to achieve the level of protection needed to prevent disease because of the varying effectiveness of the wide array of available products and the complexities of tick biology and ecology. Taking the One Health approach (shown in Figure 3) can help shift the onus of tick control away from individuals by supporting local and professionally staffed integrated tick management programs while continuing to encourage individual prevention activities (L. Eisen, 2020; Stafford et al., 2017).

Integrated tick management programs are based on the classic integrated pest management model, which involves the selection, integration, and implementation of several pest control actions based on predicted ecological, economic, and sociological consequences. According to the National Integrated Pest Management Roadmap, the purpose of Integrated Pest Management is to

- Minimize the risk to people, property, infrastructure, natural resources, and the environment;
- Reduce the evolution of pest resistance to pesticides and other pest management practices; and
- Prevent unacceptable levels of pest damage.

For tick-borne diseases, integrated approaches are designed to exploit ecological weaknesses between host, vector, and pathogen, and within their interfaces with the local environment (Figure 4). Tactics that target multiple interactions in this system can be integrated into sound environmental management strategies applied over sufficiently large areas to inhibit tick population growth and dispersal. This is best accomplished using practices reflecting local and regional factors that influence tick populations and pathogen transmission patterns. They can include targeting of multiple life stages of the tick; result in reduced pesticide loads dispersed into the environment; and be applied at different spatial scales (individual yards vs. neighborhoods and communities). These practices may also result in a slower development of pesticide-resistant ticks.

Figure 4: *Ixodes scapularis* Life Cycle



Source: Centers for Disease Control and Prevention. Retrieved on October 6, 2020 from https://www.cdc.gov/ticks/images/gallery/Iscapularislifecycle.jpg

The tick life cycle involves multiple ecological relationships between the ticks themselves, the pathogens they carry, the hosts they infect, and the physical environment, including seasonal and climate variability. Integrated tick management (ITM) exploits weaknesses in that system to reduce the reproduction and spread of ticks and minimize their interaction with humans and other hosts.

A number of strategies exist today that have shown promise on a local scale. These include strategies for integrated management, including deer removal, treatment of deer with acaricides using, for example, the USDA 4-poster device (Wong et al., 2017), and other technologies developed by private companies. However, integrated tick management remains to be validated for area-wide implementation in public health programs. Therefore, implementation research is needed to prove the utility of this approach to prevent human disease (Invasive Species Advisory Committee, 2019; Pérez de

León, Mitchell, Miller, & Lohmeyer, 2020). Novel tick control measures, such as precision vector control methods, genetic approaches, anti-tick vaccines for deer and small mammals, and other emerging technologies also hold promise for minimizing the threat of tick-borne diseases and conditions; yet, avenues to advance the technology on a larger scale are deficient. Similarly, implementation research is required for their validation under field conditions.

White-tailed deer are the key host for the adult stage of blacklegged ticks. Deer populations are expanding rapidly and are likely to continue to increase. Reasons include

- A significant decrease in predators, such as wolves, which have historically kept them in check;
- A decrease in hunting activity; and
- Changes in human land use, creating favorable conditions for deer.

Keeping their populations in check is a key factor in controlling ticks (Telford, 2017). Other important tick hosts include small mammals, reptiles, and migratory birds.

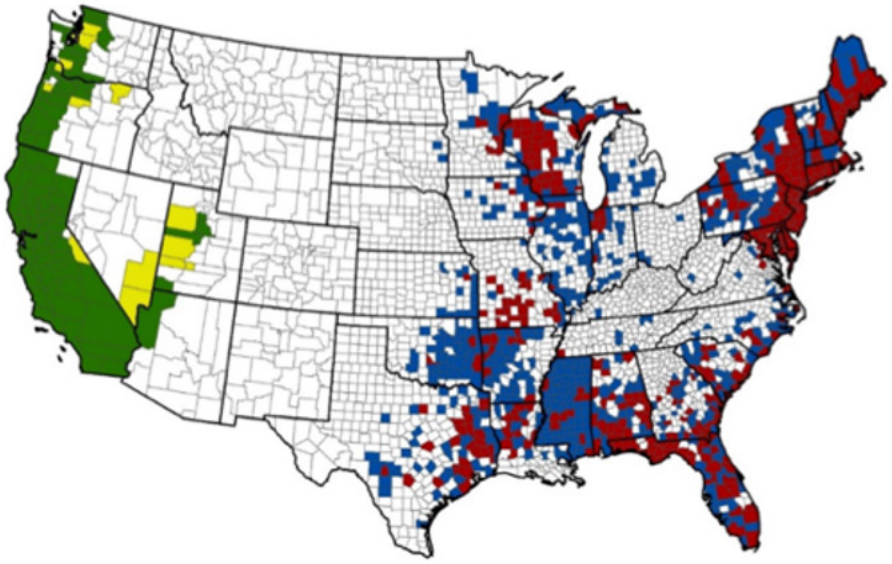
Each host interacts with ticks, pathogens, and the environment in unique ways. Therefore, extensive research is needed to better understand organisms, their relationships, and the external factors—including geography, climate, human activity, and structure of the built environment—that affect them. Genomics, functional genomics, next generation sequencing, and proteomics have been applied successfully to analyze tick microbiomes; and molecular techniques can be used to identify tick-associated microbes, known disease-causing agents, or microbes that have the potential to become emerging pathogens of medical importance.

Build on the CDC National Tick Surveillance Framework

In its 2018 Report to Congress, the Tick-Borne Disease Working Group identified as a major priority the establishment of a coordinated national tick surveillance program. While individual states had already been conducting tick surveillance in some form, the collection processes were varied, and the resulting data disparate and patchy. Nevertheless, the data enabled CDC to generate maps (Figure 5) that show changes over time in the geographic range of the Lyme disease vectors, the blacklegged or deer tick (*Ixodes scapularis*) and the western blacklegged tick (*Ixodes pacificus)*.

Figure 5: Previous Efforts by CDC to Collate National, County-scale Data: 1996 vs. 2020

1996 – Distributions of *Ixodes scapularis* and *Ixodes pacificus* in the U.S.

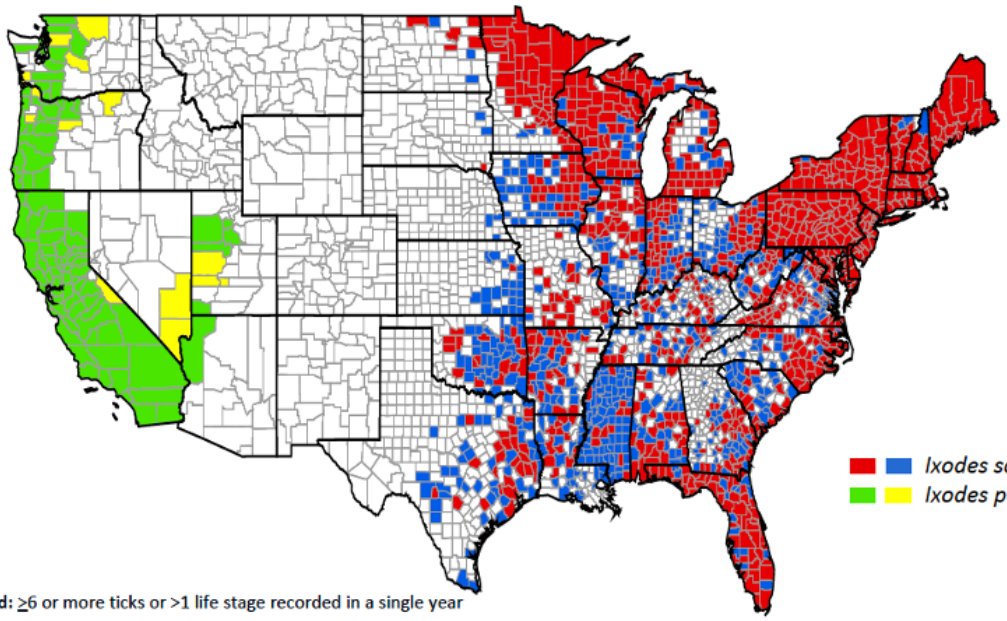


Established; ≥ 6 individuals or ≥1 life stage recorded in a single year

Reported; < 6 individuals of a single life stage recorded in a single year

Dennis et al., 1998 *J Med Entomol* 35, 629-38

2020 – Distributions of *I. scapularis* and *I. pacificus* in the U.S.



Established: ≥6 or more ticks or >1 life stage recorded in a single year

Reported: <6 individuals of a single life stage recorded in a single year

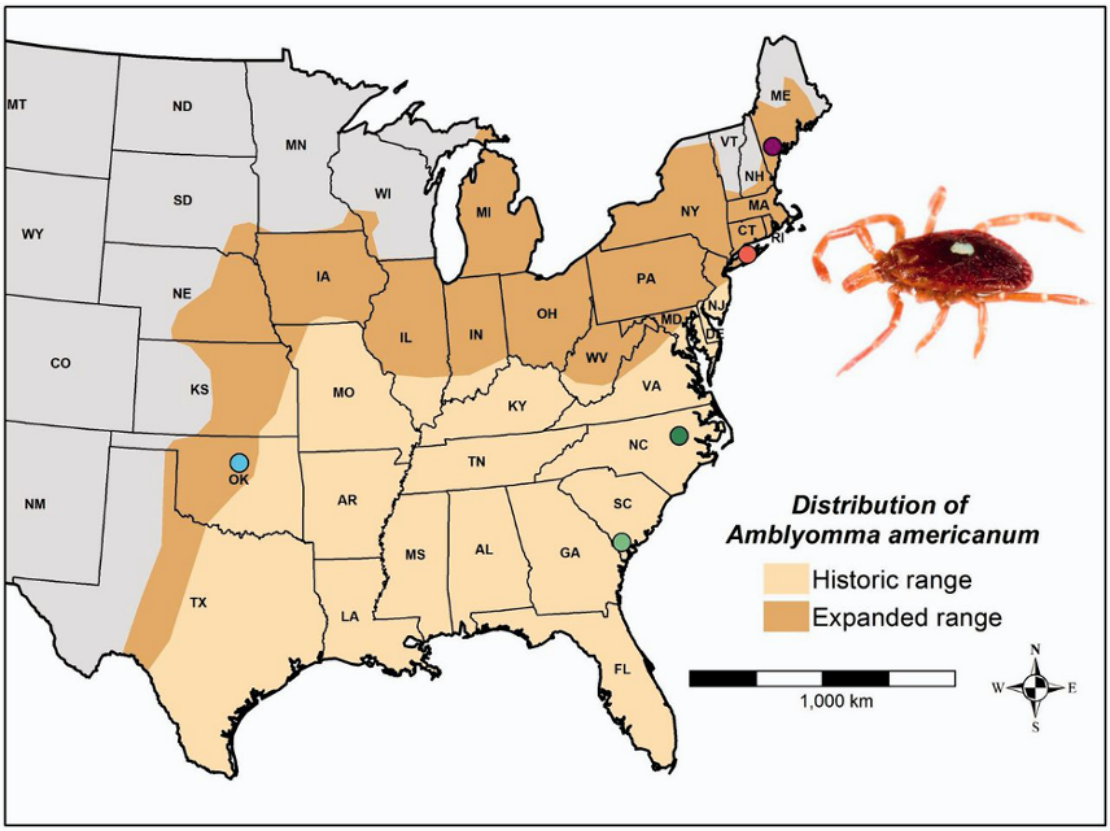
*Source: CDC, ArboNET, February 2020

In 2018, CDC began taking important steps to initiate a national tick surveillance program that aims to identify common goals and standardize tick surveillance efforts. Specifically, CDC

- Released surveillance guidance documents for two significant vectors of tick-borne diseases (blacklegged ticks and western blacklegged ticks);
- Increased financial investments in order to fund tick surveillance programs in 25 jurisdictions;
- Began pathogen testing of blacklegged and western blacklegged ticks submitted by state, local, and territorial health departments; and
- Established a system (ArboNET) that allows states to report findings directly to CDC for inclusion in the annual tick surveillance reports (C. B. Beard, personal communication, 2020; CDC, 2020h). The 2020 distribution map in Figure 5 represents a graphic depiction of ArboNET data, which is continuously updated and published annually.

Using the comparable data thus far collected, CDC has begun classifying human-biting ticks and pathogens by county, as well as estimating their densities. Starting first with the blacklegged tick, the agency plans to expand the system to include a wider range of ticks that cause human disease (L. Eisen, 2020), including the lone star tick (Figure 6). Supporting and enhancing this existing framework is critical to minimizing the public health risk of tick-borne diseases and conditions because the data collected provide a benchmark against which to measure the success of any prevention and control activities undertaken.

Figure 6: Historic and Current Expanded Distribution of Lone Star Ticks (*Amblyomma americanum*)



Source: *Genome Biol Evol*, Volume 8, Issue 5, May 2016, Pages 1351–1360, https://doi.org/10.1093/gbe/evw080

Historic and current expanded distribution of *Amblyomma americanum*, showing sampling locations in ME, NY, OK, NC, and SC. Historic range from Bishopp and Trembley (1945). Expanded range from Barrett et al. (2015), Cortinas and Spomer (2013), and Springer et al. (2014). Photo credit: J.P. Lawrence.

In addition to surveillance for the blacklegged tick (*Ixodes scapularis*) and the western blacklegged tick (*Ixodes paci icus*), tracking is critically needed for other ticks of public health importance. This includes the lone star tick (*Amblyomma americanum*) whose geographic distribution is predicted to continue its expansion as global temperatures rise (Raghavan, Peterson, Cobos, Ganta, & Foley, 2019; Sonenshine, 2018) and the invasive Asian longhorned tick (*Haemaphysalis longicornis*) (Beard et al., 2018). *Amblyomma americanum* is known to transmit five pathogens of public health importance and is the principal tick associated with Alpha-gal Syndrome, a potentially life-threatening allergy to red meat and other mammal-derived products.

Major Challenges and Issues

National-scale tick surveillance requires a process for strategic allocation of funding and a mechanism for overcoming the disparate nature of surveillance data. CDC has taken important steps to address these issues, and those should continue to be supported.

The major challenges associated with integrated tick management include effectiveness, scale, cost, and implementation. Validation of techniques can help overcome the issues of effectiveness, scale, and ultimately cost once integrated tick management methods can be broadly deployed. The development and distribution of best practices guidance and training for private, professionally staffed integrated tick management companies will help overcome the issue of implementation.

Other barriers and gaps include the following:

- Social unacceptability of deer management (Telford, 2017);
- Unwillingness to pay for effective tick control measures (L. Eisen, 2020);
- Lack of funding for large-scale neighborhood/community/area-wide studies (Fischhoff, Bowden, Keesing, & Ostfeld, 2019);
- Public distrust of chemical pesticides and repellents combined with pesticide resistance and pollinator concerns (Quadros, Johnson, Whitney, Oliver, & Chávez, 2020);
- Declining public health entomology workforce and lack of funding to support employment to sustain continued tick-borne disease prevention research (Connelly, 2019); and
- Lack of municipal/local vector control efforts specifically aimed at ticks (L. Eisen & Stafford, 2020).

Effective control of ticks and their associated disease agents requires broader acceptance and use of current technologies, improved approaches, and additional resources to scale up many of these methods, as well as the development of an organizational structure for addressing the tick problem at a community level or broader scale. New methods and products, including those with a One Health approach, in addition to controlled field trials that measure human outcomes (tick encounters and/or tick-borne disease incidence), are also urgently needed.

Recommendations

The Working Group identified the following three recommendations to minimize the public health threat of tick-borne diseases and conditions. All of the proposed actions require additional funding, which should be appropriated so that it is commensurate with the burden of tick-borne disease. Funds should be allocated to the National Institutes of Health, Centers for Disease Control and Prevention, and other Federal agencies, such as the U.S. Department of Defense and the U.S. Department of Agriculture, to support laboratory investigations and field trials to minimize Lyme disease and other

tick-borne diseases as public health threats. The cognizant Federal agencies can use existing peer-review processes to review proposals, fund meritorious projects, and evaluate progress in achieving this goal.

Recommendation 3.1: Implement multi-agency, ecologically-based One Health efforts on tick-borne diseases that promote research and enhanced vector surveillance to identify and validate integrated tick management in keystone wildlife hosts, particularly white-tailed deer, and the sustainable management of their populations.

The emergence of ticks and tick-borne diseases varies over space and time, both in the U.S. and globally. This dynamic state of flux challenges our ability to predict changes, requiring constant monitoring of the abundance, prevalence, and distribution of existing pathogens and detection of new ones through a strong surveillance/monitoring system. A strong understanding of the ecological drivers, coupled with constant data acquisition, is needed to detect public health threats in a timely fashion, raise public awareness of the threats, and develop effective disease and vector control measures (Dantas-Torres, 2015; Ostfeld & Brunner, 2015; Pérez de León et al., 2012; Randolph, 2010; Stone, Tourand, & Brissette, 2017).

Extensive research on tick control methods has provided diverse approaches to tick management. However, there have been few broad-scale projects that have tested control methods in the following ways: 1) with appropriate controls, 2) in various combinations with assessment of effectiveness as a function of cost, or 3) interactions among different control methods. Furthermore, most of these programs are without modeling frameworks to assess cost effectiveness of different interventions. Such studies would allow optimization of integrated tick management programs in terms of cost effectiveness and should include the interests of stakeholders with regard to environmental effects of the management programs.

Research to develop new control technologies and testing in appropriate locales is needed to provide tools for improved management (R. J. Eisen, Piesman, Zielinski-Gutierrez, & Eisen, 2012; Ginsberg & Couret, 2019; Kilpatrick et al., 2017). Tick control would be most effective when interventions are targeted, integrated, and implemented on a broad enough scale in time and space to lower disease incidence.

Recommendation 3.2: Minimize the public health threat of Lyme disease and other tick-borne diseases through special funding for integrated tick management, disruption of tick biological processes that contribute to pathogen transmission, and support of public-private partnerships to develop and promote tick control strategies.

Substantial reduction of Lyme disease will require a combination of modern genetic tools, modern vaccines, and by intervening into the most vulnerable elements of tick-host-pathogen processes to minimize abundance of the tick vectors, as well as block survival and multiplication of the pathogen. When implemented together, these interventions will effectively minimize transmission of Lyme disease spirochetes to humans and companion animals below the level of a public health threat.

Local and regional vector management programs offer the potential for sustainable programs that would include long-term surveillance of locally important vectors and well-targeted and optimally effective management interventions. Local and regional planning and design of tick control programs allows input by local stakeholders (including government agencies and people with interests in public health, environmental conservation, and community planning) to contribute to the design of vector and pathogen management programs. This approach can create public acceptance of appropriate interventions, as well as long-term attention to vector management in local planning and decision-making.

The Cattle Fever Tick Eradication Program, established in 1906, is an example of how Federally supported public-private partnerships can be leveraged to overcome financial barriers and facilitate the development of integrated tick management strategies that benefit multiple stakeholder groups (USDA, 2020). Tick disease vectors were eliminated from the U.S. to eradicate cattle fever, or bovine babesiosis, with the exception of a permanent quarantine zone along the transboundary region in South Texas that buffers fever tick incursions through infested stray animals, white-tailed deer, and nilgai, which wander from northeast Mexico (Esteve-Gasent et al., 2020). Spillover of cattle fever tick outbreaks beyond the permanent quarantine zone in the U.S. requires continued research to develop sustainable technologies that prevent the emergence of bovine babesiosis in the U.S. (Showler & Pérez de León, 2020). Collaboration between the USDA and multiple international partners resulted in an integrated One Health approach enabling the use of an anti-cattle fever tick vaccine by the Cattle Fever Tick Eradication Program (Pérez de León et al., 2018).

Recommendation 3.3: Provide funding to support CDC-directed expanded tick surveillance and promoting the development and implementation of best practices for integrated tick management, capturing human tick bite events, and streamlining education, training, and coordination amongst relevant Federal, state, and local agencies.

The Tick-Borne Disease Working Group recommends continuous and expanded support of the CDC national tick surveillance program. Ultimately, the network should encompass working relationships across Federal (such as CDC, DoD and USDA), state, and local agencies and vector control districts, academic institutions, land grant university agricultural experiment stations, and state, county, and local public health departments. The reach and focus of these components and their activities must be to the local community level and be structured for integration of activities based upon tick ecology inherent to the locale. Tick surveillance data serve as the information source for partnerships across these key stakeholders and for education, innovation, and design of effective integrated tick management.

Integral to these core components in defining and supporting the mission and activities of the network is engagement of stakeholders, advocacy groups, scientists from diverse disciplines, and the general

public. The national network should have a mandate to address all vectors and vector-borne diseases of public health importance. This approach brings together within one framework broad expertise, infrastructure, resources, educational expertise, and the ability to implement integrated control responses to vectors and vector-borne pathogen threats to medical and/or veterinary public health. The biology and ecology of disease vectors and zoonotic nature of many vector-borne diseases, particularly those caused by pathogens transmitted by ticks, require a One Health approach to control them sustainably.

The national tick surveillance network should ultimately provide a platform for testing all the possible interventions that are recognized, as well as emerging novel ones. This network will also serve as a framework for providing professional and public education opportunities.

For a detailed list of existing and potential integrated tick management tactics and strategies, see the Tick Biology, Ecology, and Control Subcommittee Report to the 2020 Tick-Borne Disease Working Group, "Control approaches and challenges for the major tick disease vectors in the United States," at the following link: https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/tick-biology-ecology-control-subcommittee-report/index.html

Chapter 4

Clinical Manifestations, Diagnosis, and Diagnostics

Recommendations at a Glance: Clinical Manifestations, Diagnosis, and Diagnostics

Recommendation 4.1: Fund research aimed at characterizing the full clinical spectrum, clinical manifestations, and potential complications of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), including identification of risk factors for severe illness and the importance of specific comorbidities, patient characteristics (age, gender, and race), immune impairment, and genetic host factors.

Recommendation 4.2: Establish and fund research for sensitive and specific diagnostic tests for acute rickettsial, ehrlichial, and anaplasmal diseases. Encourage development of these tests as *in vitro* diagnostics approved by FDA.

Recommendation 4.3: Establish and fund research for sensitive and specific diagnostic tests for the broader range of tick-borne diseases, including tick-borne relapsing fever, Powassan virus, and other emerging tick-borne pathogens. Encourage development of these tests as *in vitro* diagnostics approved by FDA.

Recommendation 4.4: Provide HHS with resources to partner with national Integrated Delivery Networks (IDNs) (for example, Geisinger, Kaiser, etc.) to conduct a pilot feasibility study to leverage Electronic Medical Records (EMRs) using Best Practice Alerts at the patient point-of-care for Alpha-gal Syndrome in endemic areas (upholding patient confidentiality).

Recommendation 4.5: Provide HHS with resources to partner with national Integrated Delivery Networks (IDNs) (for example, Geisinger, Kaiser, etc.) to conduct a pilot feasibility study to leverage Electronic Medical Records (EMRs) using Best Practice Alerts at the patient point-of-care for rickettsial diseases, ehrlichiosis, and anaplasmosis in endemic areas (upholding patient confidentiality).

Background

The 2019-2020 Tick-Borne Disease Working Group evaluated a broad range of tick-borne diseases and conditions that are posing increasing threats to public health in the U.S. Caused by different tick-borne pathogens carried by various tick species, these diseases and conditions present with a wide range of clinical manifestations and affect patients with varied severity. While some patients experience mild or subclinical infections after tick bites, others suffer serious clinical manifestations, and some may die if not diagnosed early and treated with appropriate medication. When dealing with these diseases and conditions, researchers and clinicians often face similar challenges and issues, including a lack of clear understanding of the clinical presentations of the broad range of tick-borne diseases and reliable diagnostic tools.

Major Challenges and Issues

Physicians rely on a combination of clinical signs, symptoms, and diagnostic test results to make a diagnosis. Many patients with tick-borne diseases do not recall a tick bite, and current diagnostic tests have limitations including low specificity and sensitivity. As a result, physicians often depend on their own knowledge to make a diagnosis. However, diagnosis based on clinical manifestations is challenging, as tick-borne diseases often present signs and symptoms similar to other diseases. Further, many clinicians lack an understanding of the spectrum of clinical presentations of tick-borne diseases to make an accurate diagnosis. The following sections discuss the challenges, issues, and needs associated with the specific tick-borne diseases.

Lyme Disease

A priority recommendation (Recommendation 5.1) of the 2018 Tick-Borne Disease Working Group Report was: Evaluate new technology or approaches for the diagnosis of Lyme disease and other tick-borne diseases. This recommendation continues to be critical for clinicians to more accurately diagnose Lyme disease, both in its earlier stages and especially in later stages when persistent symptoms continue to affect some patients, resulting in frustration for both patients and healthcare providers because of the absence of definitive means to determine if the continuing symptoms are due to continuing infection or to other yet-to-be-defined causes.

Studies utilizing animal models of infection (Elsner, Hastey, Olsen, & Baumgarth, 2015; Embers et al., 2017; Hodzic, Imai, Feng, & Barthold, 2014; Straubinger, 2000) support the hypothesis that the ongoing symptoms in patients with unresolved Lyme disease may be due to persistent infection. Some animal studies, including those using a nonhuman primate model, demonstrate that the persisting bacteria are active and induce host responses months after the initial infection and standard treatments (Greenmyer, Gaultney, Brissette, & Watt, 2018; Hodzic, Imai, & Escobar, 2019). However, the actual causes of these ongoing symptoms remain to be defined. Possible explanations include 1) direct effects of spirochete

components on host functions, 2) persisting bacterial components that result in immune or autoimmune reactions, 3) a combination of both possibilities, or 4) other yet-to-be-discovered pathophysiologic events. Although the results of these animal and non-human primate studies conducted thus far support the hypothesis that these results apply to patients with persisting Lyme disease, additional research is urgently needed to confirm or refute their relevance.

Assessment of the clinical presentation of patients with persistent symptoms associated with Lyme disease involves a complex differential diagnosis that includes chronic fatigue syndrome, fibromyalgia, Gulf War Illness, and other multi-symptom infectious and noninfectious diseases and disorders (Table 2; Donta, 2002).

Table 2: Clinical Symptoms Associated with Lyme Disease and Lyme-like Illnesses

Symptom	Lyme Disease	Chronic Fatigue Syndrome	Fibromyalgia	Gulf War Veterans' Illness*
Fatigue	+	+	+	+
Muscle pain	+	+	+	+
Joint pain	+	+	+	+
Memory loss	+	+	+	+
Confusion	+	+	+	+
Mood changes	+	+	+	+
Headache	+	+	+	+
Paresthesias	+	?	+	+
Sore throat	+	+	?	+
Sore lymph nodes	+	+	?	+
Sleep disorder	+	+	+	+
Abd pain/ diarrhea	+	?	?	+

Symptom	Lyme Disease	Chronic Fatigue Syndrome	Fibromyalgia	Gulf War Veterans' Illness*
Urinary frequency	+	?	?	?
Fevers/Sweats	+	+	?	+
Palpitations	+	?	?	+
Rashes/Sores	+	?	?	+
Weight gain	+	+	?	+

* Gulf War Veterans' Illness refers to chronic fatigue-like illness in Veterans returning from the Persian Gulf War of 1990-1991.

Existing laboratory tests provide limited value in supporting the clinical diagnosis. Serologic tests such as enzyme-linked immunosorbent assays (ELISAs) offer indirect evidence of exposure to *B. burgdorferi* and are frequently negative in patients with persistent symptoms of Lyme disease. The reasons for this are unclear but may be due to more muted immunologic responses in some patients with this form of Lyme disease. Other more direct tests (for example, PCR-DNA, culture) are insufficiently sensitive, either because the remaining organisms are not in the traditional sites sampled for analysis, or because the bacterial load is too low to be detectable, or both. Development of direct detection tests is greatly needed to address this gap. To achieve this goal, there is a need to identify better indicators of any ongoing infection or of alternative causes of the persistent symptoms.

Furthermore, issues associated with current immunological diagnostic tests is the interpretation that, in contrast to its value in confirming the diagnosis of early Lyme disease, any immunoglobulin M (IgM) reactivity in patients with persistent symptoms associated with Lyme disease is to be considered a false-positive often because those tests are not sufficiently specific to distinguish between an ongoing infection by the Lyme bacteria and possibly other unknown causes. Indeed, evidence of persistent IgM responses in animals with persisting organisms (Elsner et al., 2015; Embers et al., 2017) suggest that the IgM responses to specific proteins of *B. burgdorferi* (for example, 23kd and 39kd proteins) frequently seen in patients with persistent symptoms associated with Lyme diseases (Donta, 1997, 2002) are compatible with ongoing *B. burgdorferi* infection. To this end, funding is critically needed to develop a more specific clinical diagnostic test.

In contrast to patients with Lyme arthritis, who have robust immunoglobulin G (IgG) responses to *B. burgdorferi* and generally do well with a limited course of antibiotic treatment, patients who are clinically diagnosed with persistent symptoms of Lyme disease frequently have limited IgG responses

to *B. burgdorferi* antigens when tested by Western blot (Donta, 2012), indicating an inadequate or ineffective host immune response to the infection. In support of this conjecture, studies in animal models have demonstrated that *B. burgdorferi* interferes with the development of normal IgM/IgG transitional responses and other innate immune system responses (Elsner et al., 2015). Furthermore, animal models (Elsner et al., 2015; Embers et al., 2017; Hodzic et al., 2014) and patients with ongoing symptoms frequently exhibit continued IgM reactivity to specific *B. burgdorferi* antigens such as 23kd (outer surface protein [Osp] C) and 39kd (Donta, 2012).

Proteins unique to patients with persistent symptoms of Lyme disease have been found in cerebrospinal fluid, as compared with patients with chronic fatigue syndrome and healthy persons (Schutzer et al., 2011). These proteins have yet to be defined and may represent host response proteins to the specific illnesses. Whether further analyses of these proteins would reveal more specific biomarkers that would be helpful in the clinical diagnosis of persistent Lyme disease remains to be determined. Other host biomarkers have been identified in patients with *erythema migrans* as presenting symptom of Lyme disease, who were treated with a standard course of doxycycline but continued to suffer from symptoms. In these patients, the levels of CCL19 and interleukin 23 remained elevated (Aucott et al., 2016). Whether use of these or other biomarkers would improve the clinical diagnosis and care of patients with persistent disease awaits further evaluation. Recent studies also suggest the potential diagnostic value of imaging modalities such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Using SPECT and PET, abnormalities in metabolic activity, blood flow, and glial cell activity in the brains of patients with persistent symptoms of Lyme disease could be demonstrated, likely explaining the neurocognitive dysfunction in these patients (Coughlin et al., 2018; Donta, Noto, & Vento, 2012; Fallon, Keilp, Prohovnik, Heertum, & Mann, 2003; Fallon et al., 2009). Of note, use of certain antibiotic regimens were followed by reversal of these defects (Donta et al., 2012; Logigian et al., 1997). Further studies are needed to assess the value of these imaging modalities in diagnosis and treatment of patients with persistent symptoms of Lyme disease.

The existing gaps in Lyme disease diagnosis underscore the critical need for the development of Lyme disease-specific diagnostics to enable healthcare providers to make an accurate diagnosis, both in earlier stages of Lyme disease, but especially in later stages when patients suffer from persistent symptoms associated with Lyme disease. Targeted funding in support of the development of such tests will result in marked improvement of patient care.

Alpha-gal Syndrome

Alpha-gal Syndrome (AGS) is an allergy to the carbohydrate galactose-alpha-1,3-galactose ("alpha-gal") that is present in lower mammals such as cows, sheep, pigs, cats, and dogs (Levin et al., 2019). People (adults and children) who develop AGS most commonly report allergic reactions after eating beef, pork, or lamb (Commins et al., 2014). Unlike more traditional food allergies, reactions to alpha-gal typically occur three to eight hours (or more) after consuming mammalian meat, and this prolonged delay frequently creates a challenge in diagnosis (Commins et al., 2014; Flaherty, Kaplan, & Jerath, 2017; Levin et al., 2019). Moreover, the diagnosis of AGS is complicated because of the ubiquitous

presence of mammalian-derived products such as gummy bears and capsules (gelatin), medications (for example, heparin and thyroid hormone), bioprosthetics (for example, porcine heart valves), surgical mesh, select vaccines, and unlabeled "natural flavorings" in countless foods (Commins, 2016).

For individual patients with AGS, symptoms may include hives, itching, redness, anaphylaxis, and gastrointestinal distress (Commins et al., 2014; Levin et al., 2019). Because additional tick bites may affect the immune response to alpha-gal, the allergic response to alpha-gal may wane four to five years later for some patients; however, this might be a state of "remission" because additional tick bites may cause the allergy to recur (Commins, 2016; Commins et al., 2011; Khoury, Khoury, Schaefer, Chitnis, & Hassen, 2018). For many patients, AGS appears to be a permanent condition.

In most cases of AGS, the diagnosis is based on a history of delayed allergic reactions that occur three to eight hours after eating non-primate mammalian meat and a positive blood test (>0.1 IU/mL) for immunoglobulin E (IgE) to alpha-gal (Commins, Jerath, Cox, Erickson, & Platts-Mills, 2016). Likely owing to the delay between allergen exposure and signs/symptoms of a reaction, the time to receive a correct AGS diagnosis was 7.1 years for nearly eighty percent (22 of 28) of the respondents to semi-structured interviews (Flaherty et al., 2017). The same interviews found that in more than 100 medical visits (including 28 emergency department and two urgent care visits), the correct diagnosis or appropriate referral for patients with AGS occurred less than 10 percent of the time.

In terms of diagnosis, skin prick tests with extracts of mammalian meats (beef, pork, or lamb) were shown to be unreliable (Commins et al., 2009). Sensitization can be investigated using intradermal skin tests to the same diluted extracts (Commins et al., 2009). There are no established criteria for the titer of alpha-gal IgE to confirm an AGS diagnosis; most clinical authorities use the cut-off of >0.1 IU/mL as a positive test result (Levin et al., 2019; Wilson et al., 2019). Additional studies are needed to understand the limitations of current diagnostic testing for AGS.

The most important group of "non-classical" symptoms of AGS are those that involve the gastrointestinal (GI) tract (Levin et al., 2019). While GI complaints are part of an allergic reaction in conjunction with hives, some patients with AGS have abdominal pain without any skin involvement (Iweala, Choudhary, & Commins, 2018). These uncommon symptoms complicate the diagnosis and can be severe (Iweala et al., 2018). There have been reports of patients with AGS who have had exploratory surgery, removal of gallbladder or appendix, and partial pancreatectomy (Commins, 2016).

Longitudinal data of patients with AGS suggest that alpha-gal IgE declines over time; additional tick bites, however, appear to lead to rises in alpha-gal IgE (Commins et al., 2011; Wilson et al., 2019). Thus, one possible reason for seronegative testing despite a history of symptoms is that a patient's alpha-gal IgE has declined below the limit of test detection yet remains clinically relevant. A second possibility is pork-cat syndrome, in which primary sensitization to cat serum albumin is associated with reactions to pork meat (Posthumus et al., 2013). Several experts suggest that seronegative patients may benefit from a diagnostic food challenge to resolve confusion (Commins et al., 2014; Iweala et al., 2018).

To overcome diagnostic challenges, advances in diagnostic tools are needed to further evaluate the prevalence of alpha-gal-specific antibodies in humans. In addition, the assignment of a diagnosis code for AGS would help accumulate more accurate prevalence data (Z91.018, allergy to other foods, is the currently used ICD 10 code). The identification of marker(s) that can correlate tick bite with clinical symptoms of AGS and associated conditions is also needed.

Rickettsial Diseases

Rickettsial diseases pose a significant impact on U.S. public health. Based on passive surveillance, more than 5,500 cases of tick-borne spotted fever group (SFG) rickettsioses were reported in 2018 (CDC, 2018c). These cases do not reflect the true incidence of infections, since many cases go unreported. At present, serologic diagnosis does not distinguish between patients exposed to the various SFG *Rickettsia* species that human-biting ticks carry in the U.S. Patients exposed to non-pathogenic rickettsiae may develop antibodies (CDC, 2020g; Dahlgren, Paddock, Springer, Eisen, & Behravesh, 2016; G. S. Marshall et al., 2003; McClain & Sexton, 2020; Sanchez et al., 1992; Straily et al., 2020) that cannot be distinguished from those stimulated by pathogenic species, including the highly virulent *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever, which results in fatality rates exceeding 20% in cases where treatment is delayed (Kirkland, Wilkinson, & Sexton, 1995).

Several hurdles exist that prevent accurate diagnosis and treatment: 1) There is no generally available test for diagnosis of acute infection; 2) knowledge and awareness of laboratory diagnostics and appropriate treatment by many physicians are lacking; 3) diagnosis based on clinical manifestations early in the course of illness is very difficult; and 4) only a limited number of antibiotics are effective (G.S. Marshall et al., 2003). The need for effective recognition, diagnosis, and treatment is especially critical given the absence of any approved vaccine to prevent rickettsial infections in humans.

The spectrum of rickettsial illnesses ranges from life-threatening to asymptomatic (Parola et al., 2013; Walker, Paddock, & Dumler, 2008). The clinical diagnosis of Rocky Mountain spotted fever, the most severe disease, is hampered by a delay in the appearance of the rash for several days after onset of fever (Helmick, Bernard, & D'Angelo, 1984; Kaplowitz, Fischer, & Sparling, 1981). In addition, those with Rocky Mountain spotted fever may have symptoms that mimic a variety of other syndromes: Gastrointestinal symptoms may resemble gastroenteritis or an acute surgical abdomen (Middleton, 1978); pulmonary manifestations may mimic pneumonitis (Donohue, 1980); and neurologic involvement may mimic meningoencephalitis by other causative infectious agents (Rosenblum, Masland, & Harrell, 1952). Finally, inconsistent history of tick exposure may dissuade a physician from considering Rocky Mountain spotted fever as a diagnostic possibility.

In addition to *R. rickettsii*, other spotted fever group *Rickettsiae* also cause disease in the U.S. (Paddock et al., 2004; Shapiro et al., 2010). However, few physicians recognize the diseases caused by these agents. For example, the diagnosis of *R. parkeri* infection is hampered by low awareness of the disease and a lack of understanding of the existence and significance of an eschar, the usefulness of the eschar as a site for collection of diagnostic samples for molecular pathogen detection and identification by polymerase chain reaction (PCR), as well as the importance and availability of molecular tests for this disease (Kelman et al., 2018; Myers et al., 2013).

The earliest symptoms of spotted fever rickettsioses are nonspecific, consisting of fever, headache, and myalgias. Laboratory abnormalities are typically undetectable at this stage. By days two to four of illness, approximately 50 percent of patients will have developed a rash (macular lesions around ankles and wrists), often subtle at this stage. Laboratory findings suggestive of the diagnosis such
as thrombocytopenia and elevated liver enzymes may be present. By days five to seven, the fever and constitutional symptoms persist, the rash becomes petechial and generalized, and laboratory abnormalities become more pronounced. If left untreated, after five days of symptoms, life-threatening complications can occur, such as sepsis, meningoencephalitis, purpura fulminans, renal insufficiency, acute respiratory distress syndrome, or other devastating complications of this infection.

Atypical presentations (for example, enteric symptoms and meningoencephalitis) are not infrequent, and providers may consider alternative diagnoses when focal symptoms predominate.

There are many limitations regarding the current diagnostic tests available to physicians (Fang, Blanton, & Walker, 2017). Currently, there are no rapid point-of-care diagnostic testing methods to ensure the accurate diagnosis of a rickettsial disease during early illness. The serologic detection of anti-rickettsial antibodies is the mainstay of laboratory testing, but detectable antibodies are generally not present in the first week of illness when patients first seek evaluation (Biggs et al., 2016). The constellation of anti-spotted fever group rickettsial antibodies in healthy persons (McCall et al., 2001; Sanchez et al., 1992; Yevich et al., 1995), the exposure to *R. amblyommatis*-carrying lone star ticks (Apperson et al., 2008; Moncayo et al., 2010; Stromdahl, Vince, Billingsley, Dobbs, & Williamson, 2008), the preponderance of single sample serologic testing, and the excessive use of improper or non-quantitative serologic diagnostic assays confounds the accurate diagnosis of acute spotted fever group rickettsial infections (Dahlgren et al., 2016).

Ehrlichiosis and Anaplasmosis

Ehrlichiosis and anaplasmosis are important human health threats caused by *Ehrlichia* species and *Anaplasma phagocytophilum,* respectively. These tick-borne bacterial infections have distinctive clinical presentations and are significantly under-recognized by primary care physicians in the United States.

Despite the increasing numbers of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) cases, clinical awareness of these diseases is low. Lack of consideration of the diagnosis of ehrlichiosis is prevalent in regions endemic for lone star ticks, and this likely contributes to underdiagnosis. In North Carolina, over 90 percent of ticks that humans encounter are lone star ticks, and yet physicians were twice as likely to test for Lyme disease (66 percent) than ehrlichiosis (36 percent) (Boyce et al., 2018). Retrospective testing for ehrlichiosis in those not tested revealed that 20.2 percent of patients in this study were positive for *Ehrlichia.* HME and HGA also have significant case-fatality rates (2.7 percent and 0.3 percent respectively).

HME often presents with a spectrum of non-specific symptoms ranging from an acute onset fever with constitutional symptoms similar to a Rocky Mountain spotted fever- or toxic shock syndrome-

like multisystem disease. Some patients develop meningoencephalitis or acute respiratory distress syndrome that can be fatal (Biggs et al., 2016). Immunocompromised patients often develop overwhelming *Ehrlichia* infection.

Current laboratory assays (for example, blood smear) and immunofluorescence antibody (IFA) serology tests for HME are insensitive for early diagnosis and unable to distinguish between related species. Nucleic acid amplification tests (NAAT) performed on whole blood is relatively sensitive for the diagnosis of HME in the acute disease stage prior to doxycycline treatment. However, there are no assays or point-of-care testing for HME that are approved by the FDA. Clinical diagnosis is usually confirmed by detection of *Ehrlichia*-specific antibodies in patient sera using serology or NAAT. Identifying the specific pathogen by serology is difficult due to a lack of standardization between laboratories and false positives due to cross-reactive antibodies to related organisms (for example, *Ehrlichia canis, E. ewingii, E. muris eauclairensis,* and *A. phagocytophilum*) (Luo, Mitra, & McBride, 2018). The development of point-of-care and reference laboratory diagnostic assays based on antigen or antibody detection is currently being investigated, and such approaches might be beneficial in the future for point-of-care testing.

Anaplasmosis is primarily a seasonal illness transmitted by a tick bite in endemic areas. Many patients do not recall a tick bite (Weil, Baron, Brown, & Drapkin, 2012). As the geographic range of ticks continues to expand and patients travel, increasing numbers of cases occur. Patients typically present with a broad spectrum of non-specific symptoms; many do not recall a tick bite. Co-infections with other tick-borne pathogens, such as *B. burgdorferi* and *Babesia microti*, have been reported.

Onset of HGA is typically characterized by acute, non-specific, constitutional symptoms such as fever, often with sweats and/or chills; malaise, fatigue, myalgias, and headache within a week of being bitten by an infected tick (Aguero-Rosenfeld et al., 1996; J. S. Bakken et al., 1996; Weil et al., 2012; Wormser et al., 2016). Children often present with abdominal pain (Sigurjonsdottir, Feder, & Wormser, 2017). Due to these varied, non-specific symptoms, many patients do not seek medical attention and clinicians may not consider HGA in the differential diagnosis. If not treated relatively early in disease, many patients need hospitalization (Aguero-Rosenfeld et al., 1996; J. S. Bakken et al., 1996; Weil et al., 2012).

Patients often have characteristic laboratory abnormalities. Approximately 80 percent of patients are thrombocytopenic and/or leukopenic at the time of initial clinical presentation (J. S. Bakken et al., 2001). Thrombocytopenia develops within a few days of symptom onset, whereas leukopenia typically develops after four to five days of illness (J. S. Bakken et al., 2001). Leukopenia is then followed by neutropenia as lymphocyte counts start to recover. As lymphopenia resolves, it may be replaced by atypical lymphocytosis. Liver damage including a mild elevation of AST, ALT, alkaline phosphatase, or LDH can occur (Weil et al., 2012). A recovered patient member of the Ehrlichiosis and Anaplasmosis Subcommittee noted his primary symptom was jaundice, which is a rare presentation. His illness went undiagnosed due to this non-specific clinical presentation underscoring how the diversity of clinical presentations associated with the illness makes a definitive diagnosis difficult.

Molecular diagnostic tests, such as NAAT, are the methods of choice for early diagnosis. NAAT performed on whole blood is extremely sensitive for the diagnosis of HGA early in disease and prior to doxycycline treatment. However, there are no FDA-approved or cleared NAATs or point-of-care tests for HGA.

Babesiosis

Babesiosis in humans can range from an asymptomatic infection to a rapidly fatal disease (CDC, 2000; Herwaldt et al., 1995). Symptoms are typically flu-like with fever, chills, sweats, myalgia, nausea, and fatigue that can be accompanied by high bilirubin, elevated liver enzymes, low hemoglobin, and low platelet counts. A cough and shortness of breath are also possible. Severe disease is more common in the elderly, immunocompromised, and asplenic patients for whom treatment can be challenging. Diagnosis can be performed by microscopy, serology, and molecular techniques. Patients may need to be tested for multiple *Babesia* species to ensure an accurate diagnosis. New technologies utilizing whole genome sequencing have led to a better understanding of *Babesia* genetics and taxonomy. Promising research is currently underway to identify more effective drugs for treating patients, particularly those who are immunocompromised.

Emerging Tick-Borne Pathogens

Tick-borne relapsing fever is caused by bacterial infections with *Borrelia* species distinct from the newly renamed *Borreliella* agents known to cause Lyme disease (Gupta, 2019). Symptoms typically include recurrent episodes of fever accompanied by headache, muscle and joint pains, and nausea.

One member of the genus *Borrelia*, *Borrelia miyamotoi*, also causes illness in humans. The illness presents with fever but usually without other specific symptoms such as a rash, other localized symptoms, or recurring fever episodes. Immunocompromised individuals are at higher risk of complications (Krause et al., 2013; Wagemakers, Staarink, Sprong, & Hovius, 2015).

Both tick-borne relapsing fever and *B. miyamotoi* disease can cause severe infections; however, these can be treated with antibiotics and rarely can be fatal. Fatality, though rare, is higher for tick-borne relapsing fever during the first febrile episode. It is unknown if these diseases have persistent infections or symptomatology, nor how co-infection may affect treatment. Neither illness is nationally notifiable in the U.S. (CDC, 2020i; Krause, Fish, Narasimhan, & Barbour, 2015).

Antibodies to tick-borne relapsing fever and *B. miyamotoi* disease do not cause positive results for either whole immunoassays or Western immunoblot tests for Lyme disease. However, C6 antibody testing for Lyme disease can react with antibodies to *B. miyamotoi* disease, resulting in a false-positive result for Lyme disease (CDC, 2020f). New approaches for the diagnosis of *B. miyamotoi* disease that utilize the variable major protein and the GlpQ protein may help increase sensitivity in early and convalescent illness (Krause et al., 2015; Krause et al., 2013). Newly developed line immunoblot assays may be useful for laboratory confirmation of tick-borne relapsing fever and *B. miyamotoi* disease (Shah et al., 2019).

Tick-borne viruses pose an important emerging human disease threat, resulting in severe illness and a small number of deaths in the U.S. each year. Most notable among these is Powassan virus, a flavivirus relative of the tick-borne encephalitis viruses (CDC, 2020e). With the geographic expansion in the U.S. of the lone star tick, *Amblyomma americanum,* other tick-borne viruses have recently been identified and appear to be emerging. These include Heartland virus and Bourbon virus (CDC, 2020j). Colorado tick fever virus, transmitted by *Dermacentor* species ticks, causes sporadic illness mainly in the U.S. Mountain West region and may rarely be transmitted by blood transfusion (Yendell, Fischer, & Staples, 2015). While other tick-borne viruses likely are present in the U.S., these four viruses represent the most significant public health threats.

Tick-borne viruses remain understudied and overlooked by physicians during differential diagnosis because of their rare, and potentially emerging nature, as well as the emphasis on more common tick-borne disease, such as Lyme disease. Diagnostic testing is only available at state or Federal reference laboratories, thereby delaying diagnosis and treatment.

As with other tick-borne agents, tick-borne viruses are zoonotic pathogens. Humans most frequently become infected through the bite of an infected tick. Some flaviviruses, such as West Nile virus and Zika virus, share many biological characteristics to Powassan virus and have been shown to persist after acute infection. Although none have been reported to date, it is possible that Powassan virus can establish a persistent infection in humans and/or be responsible for birth defects, but more research is required to answer these questions.

Tularemia is caused by the bacterium *Francisella tularensis*. It is harbored in animals and can be transmitted to humans through a number of different pathways including the bites of infected ticks or deer flies, skin contact with infected animals, consuming contaminated food or water, or inhaling contaminated aerosols or dusts (CDC, 2017). The symptoms of tularemia can vary greatly depending on the route of exposure. Forms of the disease include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal (CDC, 2017). The most serious form of infection is pneumonic, which can be rapidly fatal if not diagnosed and treated promptly. Over 70 percent of reported cases are either ulceroglandular or glandular, generally indicating that the infection was caused by the bite of an infected tick or deer fly (CDC, 2020k; Ellis, Oyston, Green, & Titball, 2002; Staples, Kubota, Chalcraft, Mead, & Petersen, 2006).

Recommendations

The Working Group identified five initiatives that the Federal government could support to significantly improve our understanding of the clinical manifestations, availability of reliable diagnostic tests, and better clinical diagnosis.

Recommendation 4.1: Fund research aimed at characterizing the full clinical spectrum, clinical manifestations, and potential complications of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), including identification of risk factors for severe illness and the importance of specific comorbidities, patient characteristics (age, gender, and race), immune impairment, and genetic host factors.

Rationale

Our knowledge of the clinical manifestations of these diseases is fragmentary. Understanding these features as well as the contribution of co-infections and the true number of asymptomatic cases is needed to improve patient diagnosis and treatment. Currently both HME and HGA are frequently confused with other tick-borne diseases or febrile illnesses making diagnostic considerations and testing more complex (Biggs et al., 2016). Clinical presentation with a febrile illness during summer months in an endemic region is often suspected to be Lyme disease before HME or HGA. Seroprevalence studies of HME and HGA indicate under-reporting, misdiagnosis, subclinical infection, or stimulation of antibodies by other agents (cross-reactivity) (Biggs et al., 2016).

Recommendation 4.2: Establish and fund research for sensitive and specific diagnostic tests for acute rickettsial, ehrlichial, and anaplasmal diseases. Encourage development of these tests as *in vitro* diagnostics approved by FDA.

Rationale

Acute rickettsial diseases can be life-threatening, emphasizing the importance of early diagnosis and treatment. There are currently only limited pathogen-specific tests for these diseases (Kato et al., 2013). Clinicians may have difficulty distinguishing these diseases based on signs and symptoms in the first three days of illness. Sensitive and specific diagnostic tests that can detect but also differentiate the disease-causing pathogens would help clinicians improve early and accurate diagnosis, and initiate timely, life-saving treatment.

Recommendation 4.3: Establish and fund research for sensitive and specific diagnostic tests for the broader range of tick-borne diseases, including tick-borne relapsing fever, Powassan virus, and other emerging tick-borne pathogens. Encourage development of these tests as *in vitro* diagnostics approved by FDA.

Rationale

Among tick-borne pathogens, tick-borne relapsing fever, Powassan virus, and other emerging tick-borne pathogens present unique challenges. They are relatively uncommonly reported or emerging; may have regional differences in distribution; and, in some cases, can result in severe illness, including death. Consequently, they may not be readily recognized clinically, particularly in cases of travel-associated infections. Delays in diagnosis and treatment may lead to more severe outcomes. While some of these diseases have a relatively stable incidence, others are emerging in both incidence and distribution with more reported cases generally occurring each year in the U.S.

The availability of sensitive and specific diagnostic tests would help 1) improve the understanding of the true incidence of tick-borne diseases, including lesser-known tick-borne diseases posing serious public health threats; 2) enhance awareness; and 3) improve accurate and early diagnosis. In addition, sensitive and specific diagnostic tests would reduce the likelihood of false positives and false negatives. Further, specific tests can help differentiate infections caused by different tick-borne pathogens, thereby helping physicians initiate treatment that is most suitable for the specific disease.

Recommendation 4.4: Provide HHS with resources to partner with national Integrated Delivery Networks (IDNs) (for example, Geisinger, Kaiser, etc.) to conduct a pilot feasibility study to leverage Electronic Medical Records (EMRs) using Best Practice Alerts at the patient point-of-care for Alpha-gal Syndrome in endemic areas (upholding patient confidentiality).

Best practice alerts can help clinicians make evidence-based decisions regarding what tests to order and what treatment regimen to initiate. Currently there is no diagnostic code for Alpha-gal Syndrome. This recommendation calls for the development of a point-of-care diagnostic tool to prompt the clinician to consider Alpha-gal Syndrome, if a patient presents with characteristic symptoms (for example, anaphylaxis at night with no history of allergy), and is living in an endemic area of Alpha-gal Syndrome.

A pilot feasibility study could help assess how such a diagnostic tool might work in terms of efficacy, potential privacy, and the development of quality measures and condition-dependent triggers. Results of the pilot study would help decide if and how similar tools should be developed for other tick-borne diseases.

Recommendation 4.5: Provide HHS with resources to partner with national Integrated Delivery Networks (IDNs) (for example, Geisinger, Kaiser, etc.) to conduct a pilot feasibility study to leverage Electronic Medical Records (EMRs) using Best Practice Alerts at the patient point-of-care for rickettsia, ehrlichiosis, and anaplasmosis in endemic areas (upholding patient confidentiality).

Rationale

For HME, the development of point-of-care and reference laboratory diagnostic assays based on antigen or antibody detection is currently being investigated. During infection, *Ehrlichia* release proteins into the blood stream that induce an immune response. Several *Ehrlichia* proteins have recently been molecularly characterized from sera of patients with acute HME (Luo et al., 2018), suggesting that such approaches might be beneficial in the future for point-of-care testing.

The traditional endemic regions where HME occurs are likely to expand as the geographic distribution of ticks increases. Due to the inaccurate perception of HME as a regional illness with limited profitability, the enthusiasm for industry to develop FDA-approved, *in vitro* diagnostic tests are limited at present. Market incentives may be required to drive development and uptake of innovative diagnostics in this area (Caliendo et al., 2013; Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, 2017).

For acute HGA, the diagnosis often relies on disease suspicion in endemic areas or among those who have traveled in endemic areas. A specific diagnosis is often confirmed through one of several techniques, such as buffy coat examination of white blood cells (Silaghi et al., 2017). Abnormalities in whole blood counts, such as thrombocytopenia or leukopenia, and liver injury tests are suggestive of HGA, but non-specific due to their similarities with HME and other tick-borne diseases (J. S. Bakken et al., 2001; Weil et al., 2012). A suspected diagnosis of HGA is confirmed retrospectively using serology. Molecular diagnostic tests, such as NAAT, are the methods of choice for early diagnosis. NAAT performed on whole blood is sensitive for the diagnosis of HGA early in disease and prior to doxycycline treatment. However, there are no FDA-approved or cleared NAATs or point-of-care tests for HGA. Culture-based diagnostic testing is and will likely remain in the research domain. A rapid point-of-care assay would make real-time diagnosis accessible.

Minority Response

There is considerable misinformation in this chapter about both the interpretation and the utility of antibody tests for making a diagnosis of Lyme disease. It is well recognized that results of antibody tests for Lyme disease often are negative in patients who develop what is by far the most common manifestation of Lyme disease, the *erythema migrans* rash. This is because in most patients, antibodies against *Borrelia burgdorferi* are not detectable until three to four weeks (and for IgG antibodies, occasionally not until five to six weeks) after the onset of the infection, while the rash typically develops within seven to 21 days (one to three weeks) after the onset of infection. However, this rarely is a problem, since the diagnosis usually can be made based on the very characteristic rash, and treatment with antibiotics is recommended at that time. Obtaining tests for antibodies in such patients is not even recommended because it is known that the results will be negative in many patients who truly have Lyme disease.

Some Lyme disease advocacy groups have falsely used this well-recognized information to claim that the sensitivity of antibody tests for diagnosing Lyme disease is poor, thereby explaining why so many patients with chronic Lyme disease have negative antibody test results. While the sensitivity is poor early in the course of Lyme disease, this is *not* true when applied to the patients at issue—patients who have had active infection with *B. burgdorferi* for many weeks, months, or even years. Patients who have had active Lyme disease for more than five to six weeks virtually always have positive antibody results for IgG.

This chapter states that patients with late stage Lyme disease who have arthritis have strong IgG antibody responses to *B. burgdorferi* (that is, have positive antibody test results), but those with persistent symptoms who are "clinically diagnosed" with Lyme disease (that is, those who have persistent, non-specific symptoms that are widely prevalent in the general population), frequently have "limited IgG responses to *B. burgdorferi*" (that is, have negative antibody test results). Unfortunately, this chapter does not consider that Lyme disease is not the cause of the persistent symptoms, the far more likely reason for the negative test results in these patients.

This chapter also states that a persistently positive IgM test result is an indication of the "inability of the host to adequately clear the infection." This is another statement without evidence to support it. It is widely recognized that IgM antibodies (for any infection, including Lyme disease) may persist for many years in patients who have been treated and cured of the infection. Moreover, false-positive IgM antibody results for *any* infection, and particularly for Lyme disease, are common.

A negative IgG antibody result with a concomitant positive IgM antibody result in a patient with prolonged, non-specific symptoms is far more likely to be a false-positive IgM result than to indicate persistent infection with Lyme disease. Indeed, the authors of this chapter even cite the example of strongly positive IgG antibody results in patients with active, untreated Lyme arthritis. Why would IgG antibodies develop in patients with Lyme arthritis (a late-stage manifestation) but not in patients with other late manifestations of active infection?

Misdiagnosing Lyme disease in patients with persistent, non-specific symptoms could lead them to receive ineffective treatments that will prolong the suffering of such patients who deserve better.

Eugene David Shapiro, MD

Chapter 5
Causes, Pathogenesis, and Pathophysiology

Recommendations at a Glance: Causes, Pathogenesis, and Pathophysiology

Recommendation 5.1: Provide HHS with resources necessary to fund basic science research and clinical research to investigate the pathology of the human immune response following tick bites (e.g., Alpha-gal Syndrome [AGS]).

Recommendation 5.2: Support the targeted funding of research to understand the role of persistence of bacteria and bacterial products in the pathogenesis and management of Lyme disease (e.g., antibiotic regimens and other therapeutics).

Recommendation 5.3: Support targeted funding opportunities for research to better inform the diagnosis, pathogenesis, and management of Lyme carditis.

Background

Tick-borne diseases pose a growing threat to public health in the U.S. The number of tick-borne disease cases reported to the Centers for Disease Control and Prevention (CDC) has rapidly increased in recent years. Infected ticks often carry multiple pathogens that may cause various human diseases. In addition to known bacteria and viruses, emerging disease-causing pathogens carried by ticks continue to be discovered in the U.S. Further, novel tick species previously present only in other parts of the world are now found in the U.S.

Despite the significant public health threat from tick-borne diseases, our understanding of how these diseases progress in affected individuals remains limited. Rapid, accurate diagnostic tools are critical for guiding optimal treatment, yet early diagnosis remains challenging (see Chapter 4 on Clinical Manifestations, Diagnostics, and Diagnosis).

Treatment options for tick-borne diseases are also limited (see Chapter 6 on Treatment). While bacterial tick-borne diseases (for example Lyme disease) can be effectively treated with antimicrobials—if diagnosed and treated early, viral tick-borne diseases are usually treated with supportive care, and non-infectious, tick-bite-associated Alpha-gal Syndrome (AGS) is managed by avoiding products containing alpha-gal (galactose-α-1,3-galactose; a sugar molecule found in most mammals except in humans, apes, and monkeys). In addition, some patients with bacterial tick-borne diseases such as Lyme disease experience persistent symptoms after a standard course of antibiotic treatment. Currently there are no vaccines against tick-borne diseases.

In order to develop improved diagnostic tools and treatment strategies, we need to understand 1) the disease-causing pathogens carried by infected ticks, 2) how those pathogens interact with the human immune system and cause infection (pathogenesis), and 3) how the infection (or in some cases, the immune response itself) leads to the wide range of signs and symptoms in humans (pathophysiology).

A better understanding of the causes, pathogenesis, and pathophysiology of tick-borne diseases would lead to the development of new and improved tick-borne disease prevention strategies, diagnostic tools, and treatment options. It could also aid in understanding why individuals respond differently to a given pathogen, and lead to development of customized treatment strategies.

Major Challenges and Issues

Overall Research Gaps and Needs

Tick-borne diseases can affect the tick-bite victim's whole body and may present many manifestations. It is therefore critical to understand the effect of tick-borne diseases on the various organ systems of the body, including the circulatory, nervous, respiratory, hepatic, and musculoskeletal systems. For example, Lyme disease can affect the heart in some patients, though the process is not well understood; Powassan virus can cause disabling or fatal meningoencephalitis (inflammation of the brain and surrounding tissue); and in some cases of tick-borne diseases, neuropsychiatric complications can persist after treatment. Tick-borne infection may also change the function of the host immune system and trigger other immune pathways, leading to the development of long-term sequelae such as Lyme arthritis and AGS. Studies of human serum (Chiao et al., 1994) and studies carried out in mouse models (Elsner et al., 2015) further suggest that the ability of tick-borne infection to suppress, subvert, or modulate the host immune system may affect response to treatment and also potentially increase the risk of developing other infections.

Within the body's organ systems, it is critical to understand 1) the specific cells or tissues to which tick-borne pathogens spread upon initial infection, 2) how the pathogens get there, and 3) the microbial and human factors that enable pathogens to migrate. Such understanding could support the development of strategies to interrupt disease processes. While it is known that many pathogens can evade or inactivate various elements of the human immune response, the role and mechanisms of

immune evasion for the various tick-borne pathogens are not fully understood. Knowing the immune evasion strategies employed by tick-borne pathogens will aid in improving prevention, diagnosis, and treatment methodologies.

Additional gaps exist in our understanding of AGS, an emergent tick-bite-associated allergy with no known causative pathogen; the role of persistence of bacteria and bacterial products in the pathogenesis and management of Lyme disease; as well as diagnosis and management of Lyme carditis, an acute, life-threatening condition.

Gaps and Unmet Needs Associated with Alpha-gal Syndrome

AGS is a tick-bite-associated allergy to the carbohydrate galactose-alpha-1,3-galactose ("alpha-gal") that is present in mammals such as cows, sheep, pigs, cats, and dogs (Levin et al., 2019). People who develop AGS most commonly report allergic reactions after eating beef, pork, or lamb (Commins et al., 2014). Unlike more traditional food allergies, life-threatening anaphylactic reactions to alpha-gal occur three to eight hours after consuming mammalian meat, and this delay creates a challenge in its diagnosis (Commins et al., 2014; Flaherty et al., 2017; Levin et al., 2019).

While the number of cases of AGS in the U.S. is on the rise, much of the disease remains unknown to patients, the general public, and healthcare providers. It is not clear how people develop adverse responses following a tick bite from the lone star tick (*Amblyomma americanum*), the primary tick species associated with AGS in the U.S. It is also unclear why some people bitten by the lone star tick develop the allergy but others do not, and why the severity of the allergic reactions varies drastically among individuals. Understanding the pathology of the human immune response following bites from lone star ticks would help address many of these unknowns and ultimately improve patient care.

Gaps and Unmet Needs Associated with Persistent Symptoms of Lyme Disease

While most patients with Lyme disease are cured if treated early with an appropriate antibiotic, 10–20 percent of patients continue to experience debilitating, long-term symptoms and signs after such treatment (Marques, 2008; Melia & Auwaerter, 2016). *B. burgdorferi*, the causative agent of Lyme disease, has been demonstrated to persist in multiple organ systems as studied in a number of animal models (Elsner et al., 2015; Embers et al., 2017; Hodzic et al., 2014; Straubinger, 2000), and in human case studies as well (Haupl et al., 1993; Hudson et al., 1998; Marques et al., 2014; Oksi, Marjamaki, Nikoskelainen, & Viljanen, 1999; Pfister, Preac-Mursic, Wilske, Einhaupl, & Weinberger, 1989; Preac-Mursic et al., 1993; Preac-Mursic et al., 1989). Although the cause of these long-term symptoms is still under investigation, the results of these and other studies support the hypothesis that they are attributed to persistent infection. It remains to be assessed whether an immune response, a lingering inflammatory process triggered by non-living bacterial components, or other causes as-yet-undefined contribute to long-term symptoms.

Gaps and Unmet Needs Associated with Lyme Carditis

Lyme carditis (inflammation of the heart) is a serious, early manifestation of Lyme disease. It occurs when *B. burgdorferi* enters the cardiac tissue through the bloodstream, generally days to weeks after a tick bite (Muehlenbachs et al., 2016). The infection and associated inflammation can impair electrical signal conduction, disrupting the normal coordinated rhythm and beating of the heart, leading to a condition known as atrioventricular (AV) block. Though AV block caused by Lyme disease can usually be corrected by antibiotics, Lyme carditis can lead to sudden death in people who remain undiagnosed and untreated (CDC, 2013).

While the incidence of Lyme carditis (0.3–4 percent) is relatively low among all Lyme disease patients, it is more prevalent in pediatric patients with Lyme disease. Incidence of electrocardiographic abnormalities in pediatric patients have been reported as approximately 30 percent (Yeung & Baranchuk, 2019).

Recommendations

Building upon the 2018 Tick-Borne Disease Working Group recommendations on the pathogenesis of tick-borne diseases, the 2020 Tick-Borne Disease Working Group identified the following additional recommendations that the Federal government could act upon to further improve the understanding of the human immunopathology following a tick bite, and to help address the unique, unmet needs of many patients, including those with AGS, persistent symptoms of Lyme disease, and Lyme carditis.

Recommendation 5.1: Provide HHS with resources necessary to fund basic science research and clinical research to investigate the pathology of the human immune response following tick bites (for example, Alpha-gal Syndrome [AGS].

Rationale

The exchange of biologically active molecules and microbiota between tick vector and vertebrate host during blood feeding is a shared feature among hematophagous arthropod vectors. The tick releases salivary factors into the skin of the host and stimulates host-derived cytokines, growth factors, complement components, antibodies, and other potentially bioactive molecules. While it is known that tick salivary factors have immunomodulatory effects in the host and play a critical role in pathogen transmission and pathogenesis, many of the individual salivary components and the mechanisms through which they act on the host remain unidentified. Also poorly understood are the immune strategies used by ticks to counter the mechanisms of vertebrate host defense, as well as the effect of these host factors on vector-pathogen interactions.

Relevant to tick-bite-associated AGS, recent work has confirmed the presence of alpha-gal in the saliva and salivary glands of lone star ticks, though it is not clear whether ticks have the innate capacity to form alpha-gal or if this antigen is derived from prior blood meals or synthesized using acquired

enzymes (Crispell et al., 2019). *Ixodes scapularis* ticks also contain alpha-gal moieties in their salivary compartment, raising the possibility that this important vector may also contribute to AGS (Crispell et al., 2019). Whether additional vectors beyond lone star ticks can be associated with AGS is an important unanswered question with significant ramifications. Understanding the mechanisms that lead to AGS following a tick bite, including the mechanisms of the human immune response, should aid in the development of relevant therapeutics and improve disease management and patient care.

The surveillance of human-biting ticks and associated pathogens is already being conducted in several labs to provide customized, individual risk assessment of pathogen exposure (Xu, Mather, Hollingsworth, & Rich, 2016; Xu, Pearson, Dykstra, Andrews, & Rich, 2019; Xu, Pearson, & Rich, 2018). Studies have also shown that the tick saliva can counteract host inflammation and immunity by injecting a plethora of pharmacologically active components into the host's skin during the probing and ingestion phases of feeding (Karim & Ribeiro, 2015; Karim, Singh, & Ribeiro, 2011). These studies have built a foundation for further efforts aimed at understanding the mechanisms that lead to AGS.

In 2019, NIH announced a funding opportunity (NIH, 2020) to support short-term exploratory research in order to understand the immune response to arthropod blood feeding. One of the suggested research topics focused on the investigation of the mechanisms that lead to AGS following a tick bite. The request was well received by the scientific community and continued funding for similar, longer-term studies from the agency would further shed light on the issue.

Recommendation 5.2: Support the targeted funding of research to understand the role of persistence of bacteria and bacterial products in the pathogenesis and management of Lyme disease (for example, antibiotic regimens and other therapeutics).

Rationale

Understanding Lyme disease pathogenesis and pathophysiology is critical for developing new and improved treatment strategies and guidelines, particularly for the management of the persistent symptoms of Lyme disease. A better understanding would also help design clinical trials investigating the safety and efficacy of novel treatment regimens.

Animal studies have shown that *B. burgdorferi* can establish persistent infections in various host species, including immunocompetent mice (Tracy & Baumgarth, 2017). It is important to better understand the initial steps in the infectious process, beginning with how the causative organisms are transmitted into the hosts, how and where they disseminate, and the genes involved in this process. In these animal models, there is no correlation between the load of *B. burgdorferi* and clinical signs of disease (Tracy & Baumgarth, 2017). Immunoglobulin (Ig) G (but not IgM) antibodies control *B. burgdorferi* tissue load, but cannot clear the infection, even when the antibodies are able to passively protect from infection in a new host. Data from these and other animal studies suggest that *B. burgdorferi* suppresses effective adaptive immunity (Buffen et al., 2016; Tracy & Baumgarth, 2017); therefore, the immune system as well as bacterial factors are key to understanding the persistence of Lyme disease. Studies of immune

function in mice (Hastey, Elsner, Barthold, & Baumgarth, 2012) and in nonhuman primates (Embers et al., 2012) previously infected with *B. burgdorferi* showed that IgM-producing cells were more frequent and persistent, results similar to those observed in human patients with persistent Lyme disease (Donta, 2002). There remains a need for further research to assess the potential linkage between observations from animal studies and human disease, and to better discern the role of bacterial persistence in the pathogenesis of Lyme disease. A greater understanding of both bacterial factors and immune responses is essential for improved clinical management of patients with persistent Lyme disease.

B. burgdorferi utilize immune evasion mechanisms to establish persistent infection in its natural vertebrate hosts. Notably, the surface expression of VlsE protein and its ability to undergo antigenic variation (Norris, 2006) are required for *B. burgdorferi* to survive and persist in the presence of a humoral antibody response (Bankhead & Chaconas, 2007). A longstanding question has been how *B. burgdorferi* achieve immune escape through sequence variation of VlsE, despite the presence of a substantial number of additional antigens residing on the bacterial surface.

B. burgdorferi peptidoglycan (the primary component of the bacterial cell wall) is thought to play an important role in the host immune response and the inflammation associated with Lyme arthritis. Synovial fluid from some patients with Lyme arthritis showed high levels of *B. burgdorferi* peptidoglycan and anti-peptidoglycan antibodies, despite a lack of evidence of ongoing infection after antibiotic treatment (Jutras et al., 2019). These results suggest that *B. burgdorferi* peptidoglycan might be a persistent antigen in Lyme arthritis (Jutras et al., 2019). Further research is needed to determine if *B. burgdorferi* peptidoglycan plays a role in the pathogenesis and pathophysiology of neuroborreliosis or of persistent Lyme disease manifestations other than Lyme arthritis.

Experiments in both murine and nonhuman primate models provide evidence that persisting *B. burgdorferi* can express certain genes and induce gene expression in the infected host (Greenmyer et al., 2018). In one model, *B. burgdorferi* spirochetes localized to the dura mater around the brain, and certain brain tissues expressed genes associated with inflammation (Divan et al., 2018). Support of further research targeting neural and other tissue responses provides an opportunity to identify a means to intervene in processes associated with *B. burgdorferi* persistence, and ultimately resolve symptoms and signs of persistent Lyme disease.

Persisting *B. burgdorferi* appear to be antibiotic-tolerant, thus providing a potential explanation for the apparent failure of certain antibiotic regimens, in particular shorter-duration treatment regimens, in the treatment of patients with persistent symptoms of Lyme disease. *In vitro* and *in vivo* data on persisting *B. burgdorferi* and the effectiveness of certain antibiotics in curing the persistent state of infection have been described (Sharma, Brown, Matluck, Hu, & Lewis, 2015). Additionally, there is evidence from recent studies of persisting *B. burgdorferi in vitro* and in mouse models that certain antibiotics, combinations of antibiotics, and non-antibiotic compounds are more effective against these persistent bacteria than currently used antibiotic regimens (Feng et al., 2019; Feng et al., 2018). Future studies are needed to determine whether these observations are applicable to the human disease. Importantly, results of extensive observational studies as well as of alternative antibiotic treatment regimens appear to demonstrate success in resolving the persistent Lyme disease state (Donta, 1997, 2003) (see also Chapter 6 on Treatment).

Recommendation 5.3: Support targeted funding opportunities for research to better inform the diagnosis, pathogenesis, and management of Lyme carditis.

Rationale

Lyme carditis occurs in approximately 1 percent of Lyme disease cases reported to CDC. The sudden fatal outcome of the condition, if not treated promptly, calls for enhanced awareness among clinicians and patients. Clinicians should consider Lyme carditis in patients suspected or confirmed to have Lyme disease who present with cardiac symptoms, including palpitations, chest pain, light headedness, fainting, shortness of breath, and difficulty breathing with exertion (CDC, 2019c; Krause & Bockenstedt, 2013).

Further studies are also needed to understand the pathogenesis of Lyme carditis, including the role of both bacterial factors and the immune system, after the bacteria enter heart tissues. Understanding the mechanisms underlying the effects of *B. burgdorferi* on the conduction system of the heart should help identify risk factors for Lyme carditis, improve diagnosis, and prevent sudden death.

The rationale for this recommendation is in line with that of Recommendation 5.1. Findings of studies investigating the role of the immune system supported by these two recommendations would enhance our understanding of the overall pathology of the human immune response following tick bites, and contribute knowledge towards improving diagnosis and treatment for the broad range of tick-borne diseases and their manifestations.

Chapter 6
Treatment

Recommendations at a Glance: Treatment

Recommendation 6.1: Encourage clinical trials on early and persistent Lyme disease.

Recommendation 6.2: Conduct laboratory, clinical, and field research to address gaps in our capacity to treat and prevent the broader range of tick-borne diseases, including particularly babesiosis, tick-borne relapsing fever, Powassan virus infection, and other low-incidence tick-borne diseases.

Background

In this chapter the Working Group describes current treatment strategies for tick-borne diseases, highlights major challenges and issues, and proposes actions to fill gaps in treatment strategies for the broad range of tick-borne diseases. In the case of Lyme disease, the focus is on persistent Lyme disease.

While most patients who are diagnosed with early, acute bacterial tick-borne disease can have symptom resolution when treated with appropriate courses of antimicrobials, patients who are diagnosed later in their illness may experience serious or life-threatening symptoms. Importantly, many patients continue to experience symptoms following initial treatment.

Early and accurate treatment of tick-borne diseases relies on prompt diagnosis and the initiation of appropriate treatment. As explained in Chapter 4 (Clinical Manifestations, Diagnosis, and Diagnostics), current diagnostic tests have limitations, and early diagnosis remains challenging for most tick-borne diseases. As a result, clinicians often rely on patients' medical history, clinical signs and symptoms, and clinicians' own knowledge to make treatment decisions, including the institution of empiric antibiotic therapy. In addition, clinicians' overall knowledge of Lyme disease and other tick-borne diseases remains low. Furthermore, there are limited treatment options for many tick-borne diseases, particularly for babesiosis in immunocompromised patients, Powassan virus infection, other tick-borne viruses, and other low-incidence tick-borne diseases.

Major Challenges and Issues

Lyme Disease

Antibiotics are the mainstay treatment for Lyme disease. While treatment of early Lyme disease is generally successful, 10–20 percent of patients suffer from relapses or persistent symptoms if not treated with appropriate courses of antibiotics in a timely fashion (Marques, 2008). Additional treatment trials are encouraged to determine if these patients could benefit from a longer period of treatment than the conventional 10- to 21-day course of antibiotics, and is part of the Working Group's recommendation. The other important part of the Working Group's recommendation concerns those patients with persistent Lyme disease, as addressed below.

Accumulating evidence from studies in different animal models have demonstrated that the causative bacteria of Lyme disease can persist and are metabolically active, despite seemingly appropriate antibiotic treatment. These findings imply that the bacteria can tolerate or otherwise avoid the deleterious effects of the antibiotics used to treat the infection. These findings also support observations by numerous clinicians that longer durations of treatment using different antibiotic regimens, including combinations of antibiotics, appear to be effective in reducing or eliminating the persistent disease.

A number of controlled clinical trials using differing antibiotic regimens for durations of one to three months have failed to show significant differences in most symptoms between patients treated with antibiotics and those treated with placebo. No significant or sustainable return to normal function was reported in either the antibiotic-treated group or the placebo group (Berende et al., 2016; Klempner et al., 2001). There have been criticisms about the design of these trials, foremost being the types of antibiotics used and the duration of treatment (Delong, Blossom, Maloney, & Phillips, 2012; Klempner et al., 2013).

In patients previously treated with antibiotics, as well as untreated patients with persistent symptoms, the challenges are to 1) prove the infection is still present, and 2) determine whether the persistent symptoms are caused by the remaining infection, the result of post-infectious sequelae, or albeit less likely, unrelated causes. In the absence of direct detection tests to answer these questions (see Chapter 4 on Clinical Manifestations, Diagnosis, and Diagnostics), clinicians need to exercise their best judgment when deciding whether to administer additional antibiotic treatment or provide supportive, symptom-based medications.

Extensive clinical observations support the possibility that other antibiotic regimens could resolve the persisting symptoms of Lyme disease. For example, tetracycline has been successful in treating patients with Lyme disease, based on its more favorable pharmacologic properties compared to its derivative doxycycline (Donta, 1997). Similar results were noted with the combination of a macrolide antibiotic and an alkalinizing agent, without which the macrolide antibiotic is ineffective (Donta, 2003; Luft, Gorevic, Halperin, Volkman, & Dattwyler, 1989; Maurin, Benoliel, Bongrand, & Raoult, 1992).

Despite these and other (Horowitz & Freeman, 2019; Liegner, 2019) published clinical observations, without controlled treatment trials to validate these observations, skepticism about the efficacy of these treatment regimens will remain. If, and until there are better markers indicating the presence or absence of infection as the cause of ongoing symptoms, healthcare providers need to exercise their judgment as to how best diagnose and treat patients with persistent Lyme disease.

One of the potential explanations for the apparent failure of certain antibiotic regimens, in particular shorter-duration treatment regimens, is the presence of antibiotic-tolerant persisting organisms. Recent literature has described the presence of such organisms, including *in vitro* and *in vivo* data on persisting *B. burgdorferi*, and reported the effectiveness of certain antibiotics, some in combination, on eradicating the persistent state *in vitro* (Sharma et al., 2015). There is also evidence from recent studies of persisting *B. burgdorferi in vitro* and in mouse models, that certain other antibiotics, especially some in combination, and other non-antibiotic compounds, are more effective against these persisters than currently used antibiotic regimens (Feng et al., 2019; Feng et al., 2018).

Potentially hampering the conduct of additional controlled antibiotic treatment trials are several factors, including the lack of a *B. burgdorferi*-specific antigen detection test or relatively specific biomarkers to document the continuing presence or absence of the organism; potential difficulties in recruiting a homogeneous group of patients as regards to duration of illness, severity of illness, and serologic status; and if trials of longer duration would include true placebo groups or would compare differing antibiotic and non-antibiotic regimens. Despite these challenges, it is possible and important to conduct targeted treatment trials as the results of these trials could make a major impact on the care of patients with persistent symptoms.

Alpha-gal Syndrome

There are currently no U.S. FDA-approved medications for AGS; therefore, allergen avoidance along with rescue medication(s) are the mainstays of management (Renz et al., 2018). Owing to the ubiquitous inclusion of mammal-derived products within both food and healthcare settings, allergen avoidance for patients with AGS can present unique challenges for management (Commins et al., 2016). There are a number of considerations in the management of AGS, including avoidance of mammalian meat, dairy products in some cases, nonmeat and nondairy food products such as gelatin, as well as certain medical products that may contain mammalian-derived components (Commins, 2020).

Rickettsial Diseases

Rocky Mountain spotted fever is one of the most severe infectious diseases with a fatality rate of more than 20 percent (Kirkland et al., 1995) among previously healthy persons, if not treated with an appropriate antibiotic. Empiric doxycycline is the most effective treatment option for patients with Rocky Mountain spotted fever and other spotted fever rickettsial infections. Some clinicians are often hesitant to prescribe it for children (Alvarez-Hernandez, Ernst, Acuna-Melendrez, Vargas-Ortega, & Candia-Plata,

2018; Mosites et al., 2013; Zientek, Dahlgren, McQuiston, & Regan, 2014) and during pregnancy (Cross, Ling, Day, McGready, & Paris, 2016). Delayed initiation of treatment for Rocky Mountain spotted fever and other spotted fever rickettsial infection is associated with adverse outcomes, including increased rates of hospitalization, intensive care unit admission, and mortality.

There is a need to improve provider recognition and empiric treatment of Rocky Mountain spotted fever/spotted fever rickettsioses at early stages of the illness (for example, prior to the onset of a rash) using doxycycline, including in children younger than eight years of age (Alvarez-Hernandez, Ernst, Acuna-Melendrez, Vargas-Ortega, & Candia-Plata, 2018; Biggs et al., 2016; Kirkland et al., 1995).

Ehrlichiosis and Anaplasmosis

Doxycycline is the antibiotic of choice for the treatment of *E. chaffeensis* infections in humans, but the optimal duration of therapy remains to be determined. Patients who have not received doxycycline have an increased risk of severe outcomes including admission to the intensive care unit, mechanical ventilation, longer hospital stays, and longer illnesses (Hamburg, Storch, Micek, & Kollef, 2008). *In vivo* studies demonstrate the clinical efficacy of doxycycline; however, clinical failures have occurred (Dumler, Sutker, & Walker, 1993; Esbenshade, Esbenshade, Domm, Williams, & Frangoul, 2010; Fishbein, Dawson, & Robinson, 1994; Ismail, Walker, Ghose, & Tang, 2012). The impact of patient demographics and clinical condition (for example, immunocompromised, children, or pregnant women) and co-infections on treatment outcome, and potential alternatives to doxycycline need to be determined.

E. chaffeensis is susceptible to doxycycline, rifampin, and thiamphenicol *in vitro* at concentrations considered achievable in human blood (Brouqui & Raoult, 1992; Rolain, Maurin, Bryskier, & Raoult, 2000). *E. chaffeensis* is not susceptible *in vitro* to a range of commonly used antimicrobial agents including aminoglycosides, cephalosporins and other beta-lactams, fluoroquinolones, macrolides, and cotrimoxazole. *E. chaffeensis* is not susceptible *in vitro* to chloramphenicol (Branger, Rolain, & Raoult, 2004; Brouqui & Raoult, 1992; Rolain et al., 2000). This gap in the spectrum of drugs that can be used complicates treatment for pregnant women. Resistance has been reported to ciprofloxacin, a quinolone antibiotic (Maurin, Abergel, & Raoult, 2001).

Current recommendations for treatment of anaplasmosis are derived from prospective and retrospective case series and case reports, and support the use of doxycycline in children, and doxycycline or tetracycline in adults. Alternatives with less evidence for successful treatment include rifampin when considering infection in pregnancy or when tetracycline antibiotics are contraindicated (for example with allergy) (J. S. Bakken & Dumler, 2016; Kimberlin, Long, Brady, & Jackson, 2018).

Babesiosis and Emerging Tick-Borne Pathogens

Treatment of babesiosis relies on the use of anti-protozoal agents and/or antibiotics, including atovaquone, azithromycin, clindamycin, and quinine. Treatment regimens are limited by the emergence of drug-resistant parasites, toxicity, and failure of drugs (Genda et al., 2016; Krause et al., 2000; Lawres et al., 2016).

Treatment failures have been observed across the Northeast, primarily in patients with associated comorbidities or immunosuppression where *B. microti* babesiosis is present. Resistance to atovaquone and azithromycin is now commonly seen in clinical practice (Lemieux et al., 2016; Simon et al., 2017; Wormser et al., 2010). Additional research is needed to identify more effective treatment protocols. Ineffective treatment can increase inflammation, and additional research is needed to better understand how to reduce cellular damage caused by inflammation.

Four tick-borne viruses are found in the United States and have begun to gain attention as individual cases are reported in the media, creating growing concern about their transmission within minutes of a tick bite. These four pathogens (Powassan virus, Heartland virus, Bourbon virus, and Colorado tick fever virus) can all cause death, some with high case-fatality rates.

Patients with severe Powassan virus disease and the other tick-borne viruses are often hospitalized. Treatment is supportive, including respiratory support, intravenous fluids, and medications to reduce swelling in the brain. No effective treatment exists for severe disease; 10–15 percent of cases are fatal (CDC, 2020e; Piantadosi et al., 2016). The potential role of corticosteroids has not been defined. Intravenous immunoglobulin for the treatment of Powassan virus encephalitis has also been tried. The role of antiviral therapy in treating Powassan virus disease is unclear.

Tularemia

Streptomycin or gentamicin (aminoglycosides) are the antibiotics of choice for the treatment of tularemia (Enderlin, Morales, Jacobs, & Cross, 1994). Ciprofloxacin has been successfully used to treat uncomplicated tularemia, and may be more effective than the aminoglycosides; however, a formal clinical trial is needed to assess its efficacy (Meric et al., 2008). Doxycycline is effective against *F. tularensis* and may prevent serious complications.

Recommendations

Recommendation 6.1: Encourage clinical trials on early and persistent Lyme Disease.

Rationale

Establishing safe and effective treatment regimens for patients with early and persistent Lyme disease remains challenging for scientists, clinicians, and patients. The results of previous clinical trials involving patients with early Lyme disease have shown that the antibiotic regimens used are highly effective in most patients, but there are a number of patients who have ongoing or relapsing symptoms. Additional treatment trials are encouraged to develop more optimal treatment strategies to help patients suffering persisting symptoms, including those whose symptoms persist despite antibiotic treatment and those who were not treated early in the disease. These could include trials using antibiotic treatments of longer duration, new drug therapies, and combination strategies.

The 2018 Tick-Borne Disease Working Group noted that additional clinical trials that include patient and physician perspectives on appropriate endpoints are required to better equip clinicians in treating the many different presentations of Lyme disease and other tick-borne diseases in order to reduce healthcare costs and decrease human suffering. However, limited prospective human studies have thus far been conducted.

Possible Opportunities

Animal studies have shown that persistent *B. burgdorferi* are capable of altering and evading host immune responses and capable of forming persister cells following certain antibiotic treatments (Embers et al., 2017; Hodzic et al., 2014). Accumulating evidence from animal studies suggests that persisting, metabolically active *B. burgdorferi* (Greenmyer et al., 2018) may be the cause of persistent symptoms in some patients who have or have not been previously treated with antibiotics. Observational human studies also suggest that certain treatment regimens might be safe and effective for treating patients with persistent symptoms of Lyme disease (Donta, 2012).

In consideration of available data from animal studies and clinical observations, the Working Group encourages the scientific and medical communities to continue investigating the pathogenesis of the disease (see Chapter 5 on Causes, Pathogenesis, and Pathophysiology) and develop hypotheses for future clinical trials.

Recommendation 6.2: Conduct laboratory, clinical, and field research to address gaps in our capacity to treat and prevent the broader range of tick-borne diseases, including particularly babesiosis, tick-borne relapsing fever, Powassan virus infection, and other low-incidence tick-borne diseases.

Rationale

Safe and effective therapeutics are needed for the treatment of all tick-borne diseases. There is also a need for better understanding of the ecology and distribution of tick-borne pathogens and their reservoirs, particularly *Babesia duncani*, tick-borne relapsing fever and *Borrelia miyamotoi* agents, and tick-borne viruses particularly Powassan virus.

Opportunity to Reduce Threats and Disease Burden Associated with Babesiosis

There is a significant opportunity to prevent transfusion-associated cases because of the introduction of FDA-approved, blood-supply-screening tests in states where tick-borne transmission of babesiosis is known to occur.

New technologies utilizing whole genome sequencing have led to a better understanding of *Babesia* genetics and taxonomy. Promising research is currently underway to identify more effective drugs for treating patients, particularly those who are immunocompromised.

Opportunity to Reduce Tick-Borne Relapsing Fever and *B. miyamotoi* Disease

Cases of tick-borne relapsing fever and *B. miyamotoi* disease are inconsistently reported in states where transmission is known to occur. Neither tick-borne relapsing fever nor *B. miyamotoi* disease is nationally notifiable. Consequently, the burden of illness in the U.S. is not known and cannot be easily determined. More information is needed about the geographic distribution of the agents that cause both tick-borne relapsing fever and *B. miyamotoi* disease. *B. miyamotoi* disease occurs in areas where Lyme disease also occurs leading to the possibility for co-infection with other pathogens. New technologies utilizing metagenomics have led to the detection of *B. miyamotoi* in patients with undifferentiated acute febrile illness.

There is increasing recognition that tick-borne relapsing fever has been relatively neglected as a disease in North America, Africa, and Eurasia. Increased funding and resources can aid in the recruitment of professionals to study the many gaps in tick-borne relapsing fever and *B. miyamotoi* disease research.

Opportunity to Reduce Diseases Caused by Tick-Borne Viruses

Increasing numbers of cases of Powassan virus infection have been reported in the Northeastern and Upper Midwestern states of the U.S. This emerging trend is similar to other tick-borne diseases associated with deer, rodents, and the blacklegged tick, *Ixodes scapularis*. In the absence of effective tick control strategies, this trend will likely continue.

Heartland viruses and Bourbon viruses are recently discovered pathogens; therefore, little is known about their natural ecology (CDC, 2019a, 2020c). There is concern that the recently introduced Asian longhorned tick, *Haemaphysalis longicornis*, which is rapidly spreading in the U.S., could be a vector for Heartland virus both between animals and to humans. The Asian longhorned tick is a vector for a virus genetically similar to Heartland virus that causes severe fever with thrombocytopenia syndrome, a potentially fatal infection in Asia. In addition to Heartland viruses, other pathogens and allergens have been shown to be transmissible by *H. longicornis*. To date, no human pathogens have been found in *H. longicornis* collected and tested in the U.S. Anecdotal evidence has shown that this tick, at least in lineages found in the U.S., does not have a preference for humans, though occasional bites have been reported (L. Eisen, personal communication, January 9, 2020).

New technology utilizing metagenomics may be useful for identifying novel tick-borne viruses in both humans and animal reservoirs. Recently initiated national tick surveillance activities may lead to a better understanding of the enzootic distribution of tick-borne viruses across the U.S.

Opportunity to Reduce the Risk of Tularemia as a Public Health Threat

Tularemia is caused by the bacterium *Francisella tularensis*. It is harbored in animals and can be transmitted to humans through a number of different pathways including the bites of infected ticks or deer flies, skin contact with infected animals, consuming contaminated food or water, or inhaling contaminated aerosols or dusts. The symptoms of tularemia can vary greatly depending on the route of exposure. Forms of the disease include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal. The most serious form of infection is pneumonic, which can be rapidly fatal if not diagnosed and treated promptly.

Each year 100 to 200 cases of tularemia are reported in the U.S. The majority of these cases occur during the summer months and are associated with outdoor exposure. Over 70 percent of reported cases are either ulceroglandular or glandular, generally indicating that the infection was caused by the bite of an infected tick or deer fly (G. F. Brooks & Buchanan, 1970).

Tularemia is classified as a U.S. Department of Health and Human Services Tier 1 Select Agent because of its potential to be used as a weapon. Significant resources have previously been provided to enhance surveillance, diagnosis, and treatment. However, the Select Agent designation has drastically limited research on tularemia.

New technology utilizing metagenomics may be useful for identifying *F. tularensis* in both humans and animal reservoirs. Recently initiated national tick surveillance activities may lead to a better understanding of the distribution of enzootic tularemia occurrence across the U.S.

Chapter 7
Clinician and Public Education, Patient Access to Care

Recommendations at a Glance: Clinician and Public Education, Patient Access to Care

Recommendation 7.1: Recommend Federal government websites and educational materials and seminars for clinicians, the public, and public health departments, which discuss Lyme disease, provide information that the state of the science relating to persistent symptoms associated with Lyme disease, is limited, emerging, and unsettled; and increase public awareness that there are divergent views on diagnosis and treatment. Consider that shared medical decision-making may be appropriate in some circumstances.

Recommendation 7.2: Fund and support a directive for CDC (or other appropriate HHS OPDIV or agency) to develop (either directly or through an approved federal contract) a multi-leveled and nationwide curriculum on Lyme disease for clinicians-in-training as well as continuing medical education modules to increase the pool of qualified and practicing clinicians. Provide funding for the U.S. military to participate in this nationwide training and education on Lyme disease and other tick-borne diseases and conditions. This curriculum should be introduced and encouraged at the State level. The final curriculum shall incorporate feedback from patients, clinicians, and research scientists with expertise/experience that represents diverse scientific and clinical experiences on the full spectrum of Lyme disease and other tick-borne diseases/conditions.

Recommendation 7.3: Fund efforts across the U.S. to expand/require medical education to inform emergency, primary care, and other healthcare providers and to raise clinician and public awareness of rickettsial (including Rocky Mountain spotted fever), ehrlichial, and anaplasmal diseases.

Recommendation 7.4: Fund efforts across the U.S. to expand/require medical education to inform emergency, primary care, and other healthcare providers and to raise clinician and public awareness of babesiosis, tick-borne relapsing fever, emerging tick-borne viral infections, and other low-incidence tick-borne diseases.

Recommendation 7.5: Generate broad awareness of Alpha-gal Syndrome through the following two mechanisms:

- Provide funding/support/resources necessary to create a National Tick-Borne Alpha-gal Syndrome Alert that is focused on awareness, prevention, and education regarding tick associated Alpha-gal Syndrome and that targets key stakeholder groups.
- Label foods/beverages, medications and medical products, cosmetics, etc. containing mammalian-derived components for the safety of consumers with Alpha-gal Syndrome.

Background

Tick-borne diseases are increasing causes of illness and disability in the United States, accounting for approximately 77 percent of all nationally reported vector-borne diseases to the Centers for Disease Control and Prevention (CDC) each year (Petersen et al., 2019). This group of illnesses is caused by bites from various species of infected ticks. Most tick-borne diseases are caused by bacteria, such as is the case with Lyme disease, which has accounted for over 70 percent of reported tick-borne diseases in the U.S. from 2016 to 2018 (Table 3). Ticks also transmit viruses and piroplasms as well as non-infectious conditions such as tick-borne paralysis and the increasingly common Alpha-gal Syndrome.

Lyme Disease

According to the National Institutes of Health (NIH), "Bacteria cause most tickborne diseases in the United States, with Lyme disease representing the vast majority (82 percent) of reported cases," and that, "The public health burden of tickborne disease is considerably underreported, according to the authors. For example, the U.S. Centers for Disease Control and Prevention (CDC) reports approximately 30,000 cases of Lyme disease annually in the U.S. but estimates that the true incidence is 10 times that number" (National Institutes of Health, 2018, July 25). This means that the CDC average of roughly 38,000 Lyme disease cases reported annually from 2016 to 2018 (Table 3) represents only about 13 percent of the true incidence of Lyme disease cases (more than 300,000) annually in the United States. Additionally, using the same CDC average of roughly 38,000 reported Lyme disease cases as part of the CDC average of roughly 52,000 total tick-borne disease cases reported annually during this same time period (Table 3), reported Lyme disease cases accounted for approximately 73 percent of all of the tick-borne cases reported annually from 2016 to 2018 as shown in this table.

Table 3: Reported Tick-borne Diseases, United States

Reported Tickborne Diseases, U.S.	2016	2017	2018
Lyme Disease (confirmed and probable)	36,429	42,743	33,666
Anaplasmosis/Ehrlichiosis	5,750	7,718	6,123
Spotted Fever Rickettsiosis	4,269	6,248	5,544
Babesiosis	1,910	2,368	2,160
Tularemia	230	239	229
Powassan virus	22	33	21
Total	**48,610**	**59,349**	**47,743**

Source: Centers for Disease Control and Prevention, *Tickborne Disease Surveillance Data Summary*. Retrieved on October 19, 2020 from https://www.cdc.gov/ticks/data-summary/index.html

Along with the increasing numbers of tick-borne disease cases, the costs attributed to Lyme disease and other tick-borne diseases are substantial and also growing. Since Lyme disease represents the majority of tick-borne disease cases in the United States, most of the research and data on cost focuses on Lyme disease, with little data on the costs of other tick-borne diseases on which to draw. However, we believe that this data can be extended to include potential and probable costs for the other reported tick-borne diseases discussed throughout this report and in this chapter. Therefore, we note that much of the data on cost presented here, while focused on Lyme disease, should also be applied to the remaining percentage of the annual reported tick-borne diseases listed in Table 1 (p. 4).

One estimate of cost shows that direct Lyme disease medical costs could represent $1.3 billion each year, with marked increases when therapy fails to return patients to their pre-Lyme disease health status (Adrion et al., 2015). The bulk of Lyme disease-related costs are due to indirect medical costs, nonmedical costs, and lost productivity. The inflation-adjusted societal cost of illness for individuals with late-stage Lyme disease is approximately $24,000 per year, with loss of productivity accounting for more than half of those costs (Johnson, 2019a; Zhang et al., 2006). It was estimated that in year 2000 dollars, the annual cost of Lyme disease in the U.S. was $203 million. With the CDC's increased estimate of annual Lyme cases (from 30,000 to 300,000) and adjustment for inflation, these costs have increased to over $3 billion annually and would far exceed this if costs were to take into account the growing number of patients who remain ill over time.

Table 4: Lyme Disease Cost Per Patient in 2006 and 2018 (Inflation Adjusted)

Costs $ (% of total)	Zhang 2006 study (inflation adjusted to Aug. 2018)	
	Early Lyme Disease	Late/Chronic Lyme Disease
Direct medical	$1,196 (61%)	$2,796 (12%)
Indirect medical	$387 (20%)	$648 (3%)
Non-medical	$78 (4%)	$7,631 (32%)
Productivity loss	$296 (15%)	$13,123 (54%)
Total	**$1,957**	**$24,198**

Cost is just one aspect of the overall burden of Lyme disease; the other is disease severity. When diagnosed early and given appropriate treatment, most Lyme disease patients make a full recovery. However, studies show that anywhere from between 10 percent and 20 percent (Marques, 2008), and up to 35 percent, of patients experience chronic, often debilitating, symptoms (Aucott, Rebman, Crowder, & Kortte, 2013). The exact cause of these symptoms is not fully understood, yet receiving an early diagnosis seems to be a key factor in whether or not a patient will make a full recovery. Moreover, delayed diagnosis appears to contribute to the risk for persistent symptoms associated with Lyme disease in many patients.

These patients with persistent symptoms associated with Lyme disease, and often with co-infections and other tick-borne diseases, experience a highly compromised quality of life. Respondents to a study of over 3,000 persistent Lyme disease patients reported very poor health-related quality of life, with 72 percent reporting fair or poor health status, significantly exceeding the 62 percent rate reported by those with congestive heart failure and the 16 percent rate of the general population (Burns et al., 1997; Johnson, 2018; Johnson, Wilcox, Mankoff, & Stricker, 2014). Also, substantial impairment of quality of life has been demonstrated in several NIH-funded clinical trials—those authored by Fallon et al. (2008), Klempner et al. (2001), and Krupp et al. (2003).

In addition, using the CDC health-related quality of life indicators, respondents in this same 3000-patient study reported a substantially higher number of bad mental and physical health days, a significant symptom disease burden, and greater activity limitations compared to both the general population as well as patients with other chronic diseases (Johnson et al., 2014).

Functional impairment for patients with persistent symptoms associated with Lyme disease is high. Many are unable to work or go to school or have reduced their work hours or changed the nature of

their work to accommodate their illness (Johnson et al., 2014). Two studies found that roughly a quarter of patients had been on disability at some point in the duration of their illness (Johnson, Aylward, & Stricker, 2011; Johnson et al., 2014). The majority reported that they had been ill for 10 or more years.

According to the Agency for Healthcare Research and Quality (AHRQ), "Registries can be used to recruit patients for clinical trials to learn about a particular disease or condition; to develop therapeutics or to learn about population behavior patterns and their association with disease development; developing research hypotheses; or for improving and monitoring the quality of health care" (Workman, 2013).

The MyLymeData patient registry, like other patient registries, provides crucial information about patients with persistent symptoms associated with Lyme disease and their clinical experiences, including their experiences accessing care and treatment and the obstacles that they frequently face in obtaining appropriate care. The MyLymeData patient registry survey items were based on registry data elements recommended by AHRQ, from prior surveys, and from peer-reviewed published literature for Lyme disease and other conditions. Additional sources of survey questions included standard government question banks such as the CDC Behavioral Risk Factor Surveillance System, National Health Interview Survey, National Ambulatory Medical Care Survey, and National Center for Health Statistics, as well as the AHRQ Medical Expenditure Panel Survey. The registry uses the same registry platform that serves NIH patient registries. The NIH lists 72 registries on its website.

Patients with persistent symptoms associated with Lyme disease face significant issues of patient access to care involving both providers and insurers, as well as the need for shared medical decision-making in the face of uncertainty regarding diagnosis and treatment. Unfortunately, patients with persistent symptoms associated with Lyme disease report that they are systematically denied access to the care they need. For example:

- Fifty percent of participants in the MyLymeData patient registry report that their clinicians do not accept insurance coverage; 26 percent report that they cannot find a clinician who treats persistent Lyme disease; and 18 percent report that they do not use antibiotics because their insurance will not cover them (Johnson, 2019a).

- Sixty-seven percent report that they have postponed or avoided medical treatment due to discrimination, disrespect, or difficulty obtaining care, and nearly half (47 percent) report that they have been denied treatment (Johnson, 2019b).

- The majority of over 2,400 survey respondents report traveling more than 50 miles and a substantial minority traveling more than 500 miles for Lyme disease treatment (Johnson et al., 2011).

- The majority (82 percent) of persistent Lyme disease patients seeking care at their local hospital report that they had difficulty obtaining treatment (Johnson et al., 2011); some hospitals deny hospital privileges to physicians and other practitioners who do not follow the Infectious Diseases Society of America (IDSA) Lyme disease guidelines (Johnson & Stricker, 2010; Stricker & Johnson, 2009; Wolfram, 2008).

- Seventy percent of patients with persistent Lyme disease report a delay of six months or more in their diagnosis (Johnson, Shapiro, & Mankoff, 2018), and a majority of patients reported seeing seven or more clinicians before being diagnosed (Johnson et al, 2011).

Other Tick-Borne Diseases and Conditions of Public Health Importance

The other tick-borne pathogens and conditions addressed in this report also present significant challenges to patients, communities, and healthcare practitioners. The ranges of the various tick vectors frequently overlap in such a way that multiple tick-borne pathogens may be present in a given locale. Some of the other tick-borne diseases and conditions, with the exception of Rocky Mountain spotted fever and ehrlichiosis, are relatively unknown to many clinicians because they are uncommon, emerging, or significantly more localized than Lyme disease.

Rickettsial Diseases

Rickettsial diseases, of which there are several, are often difficult to diagnose early in the course of the infection. Most have undifferentiated signs and symptoms and a variable spectrum of severity, which often makes them difficult to distinguish from other infections. Clinician awareness and ability to recognize these diseases is low and diagnostic testing in the acute stage is lacking. Clinician understanding regarding appropriate therapies, especially for young children, is limited.

Delayed initiation of treatment for Rocky Mountain spotted fever and other spotted fever rickettsial infections is associated with adverse outcomes, including increased rates of hospitalization, intensive care unit admission, and mortality. Multiple studies indicate that the most important factor in failure to prescribe empiric doxycycline is not a delay in seeking health care, but rather a failure of providers to consider the diagnosis of spotted fever rickettsial infection, particularly during the first few days of illness when empiric therapy is most effective at reducing morbidity or mortality attributable to these diseases (M. A. Hattwick et al., 1978; Kirkland et al., 1995; Mosites et al., 2013).

Ehrlichial and Anaplasmal Diseases

According to CDC, the case-fatality rate for ehrlichiosis patients is "roughly 1 percent" (CDC, 2020b) and is less than 1 percent for anaplasmosis patients (CDC, 2020a). Despite the case-fatality rates, these diseases are often under-recognized by primary care clinicians in the United States. Discussion of an example of this issue can be found in a North Carolina study where researchers indicate that human monocytic ehrlichiosis (HME) is frequently confused with other tick-borne diseases or febrile illnesses, making diagnostic considerations and testing more complex. Clinical presentation with a febrile illness during summer months in an endemic region is often suspected to be Lyme disease or Rocky Mountain spotted fever before HME or human granulocytic anaplasmosis (Boyce et al., 2018).

Under-reporting and misdiagnosis are the two most common problems associated with these diseases. A survey of U.S. patients found that while 50 percent were familiar with Lyme disease, only 1.4 percent were familiar with ehrlichiosis. North Carolina clinicians were found to be more likely to test for Lyme disease (66 percent) than ehrlichiosis (36 percent) (Boyce et al., 2018) even though residents were nine times more likely to encounter lone star ticks, the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, than blacklegged ticks. Moreover, retrospective testing for ehrlichiosis in those not tested revealed that 20.2 percent of patients in this study were positive for *Ehrlichia*.

It is important to note here that the blacklegged tick can be a potential vector for *Ehrlichia muris eauclairensis*, and despite the blacklegged tick being "…widely distributed in the eastern United States," *E. muris eauclairensis* "infections have only been reported from Wisconsin and Minnesota and travelers to those states" (CDC, 2019b).

Babesiosis, Tick-borne Relapsing Fever, Emerging Tick-borne Viral Infections, and Low-incidence Tick-borne Diseases

Similar to rickettsial, ehrlichial, and anaplasmal diseases, there are several other under-recognized and frequently misdiagnosed tick-borne diseases and infections that produce an array of signs and symptoms. Important features and information regarding these diseases that the public and clinicians need to be aware of, include, but are not limited to, the following:

- *Babesia* has been found to be transmitted through the blood supply (CDC, 2018a), and it is only recently that tests have been licensed and put into place to screen for *Babesia* species (U.S. Food and Drug Administration, 2019).
- Babesiosis in humans can range from an asymptomatic infection to a rapidly fatal disease.
- Tick-borne relapsing fever can cause severe infection with the fatality higher during the first febrile episode.
- Emerging tick-borne viruses, including Powassan virus, Heartland virus, Bourbon virus, and Colorado tick fever virus can result in severe illness and a small number of deaths in the U.S. each year.
- Tularemia is characterized by several distinct forms (Council of State and Territorial Epidemiologists, 2016). Complications are more frequent in those who do not seek prompt medical attention (Penn & Kinasewitz, 1987). Tick-transmitted tularemia is often undiagnosed due to a mild and self-limiting fever and adenopathy (Schmid et al., 1983).

As is the case with most, if not all, tick-borne diseases, lack of recognition results in diagnostic and treatment delays and thus, more severe outcomes. Immunocompromised individuals are at higher risk of complications.

Alpha-gal Syndrome

Alpha-gal Syndrome (AGS) is an allergy to the carbohydrate galactose-alpha-1,3-galactose that is present in lower mammals such as cows, pigs, and sheep. Unlike more traditional food allergies, allergic reactions after consuming mammalian meat and/or products derived from mammals are delayed by three to eight hours, increasing the likelihood of a missed diagnosis. Thus, clinician awareness of the syndrome and its associated delay in allergic reaction is key to making the diagnosis.

AGS may have a significant impact on patient quality of life. The only treatment currently available is avoidance of the allergen; hence, the patient must commit to a life-long change in eating habits and sustained vigilance about the products and ingredients to which they are exposed. This is especially challenging for patients with AGS because the Food Allergen Labeling and Consumer Protection Act of 2004 ("FDA Food Allergen Labeling and Consumer Protection Act," 2014) does not currently include alpha-gal. Patients with AGS are often unable to determine if a product contains mammalian-derived ingredients. Some manufacturers use the term "proprietary ingredients" as a catch-all for many ingredients that could put patients with AGS at risk, and FDA does not require medical product manufacturers to report or describe food allergens in labeling. The consequences of the lack of alpha-gal labeling can be life-threatening and even fatal.

Numerous public commenters to the Tick-Borne Disease Working Group report frequently experiencing allergic reaction, even anaphylaxis, because they are unable to determine the composition of many common products and medications. They report experiencing severe emotional and physical strain caused by the ever-looming threat of allergic reaction, and they often struggle to obtain reasonable accommodations to continue gainful employment or attend school (Platt & Carrison, 2019).

AGS prevention strategies should be focused on awareness and education. Currently, general public knowledge is limited regarding lone star ticks, allergic reactions such as AGS, and the implications of the syndrome (Commins, 2016; Flaherty et al., 2017). Many patients with AGS learn about their condition through Google, friends, news, or social media rather than through healthcare providers. Educational materials and proper guidance are lacking for patients who have been diagnosed with AGS or who suspect they have it. They are often left to their own devices for education and ongoing management.

Recommendations

In developing the following recommendations for Congress in this chapter of the report, the Working Group has focused on the gaps both in access to care for patients with Lyme disease, and patients with other, less prevalent tick-borne diseases. Additional focus has been given to clinician education regarding Lyme disease and the other tick-borne diseases as a critical element of both initial clinician training prior to beginning clinical practice as well as their ongoing training once established in clinical practice. The Working Group has identified the following important initiatives, which the Federal government could undertake to markedly improve access to care for these patients and to comprehensively improve existing clinician education for the great numbers of physicians and advanced practice providers across the country who will need this essential knowledge base to accurately diagnose and provide compassionate care and effective treatment for these patients now and in the future.

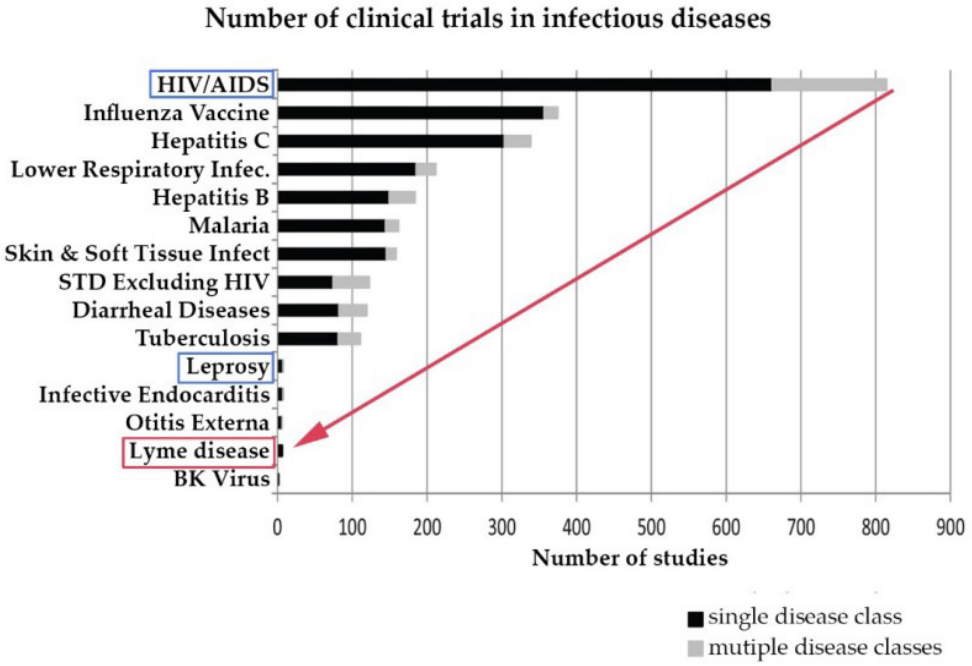
Recommendation 7.1: Recommend Federal government websites and educational materials and seminars for clinicians, the public, and public health departments, which discuss Lyme disease, provide information that the state of the science relating to persistent symptoms associated with Lyme disease, is limited, emerging, and unsettled; and increase public awareness that there are divergent views on diagnosis and treatment. Consider that shared medical decision-making may be appropriate in some circumstances.

Limited, Emerging, and Unsettled State of the Science Relating to Persistent Symptoms Associated with Lyme Disease

In Lyme disease, uncertainty arises from two factors: the lack of a robust evidence base and the heterogeneity of patient clinical presentation and treatment response (Cameron, Johnson, & Maloney, 2014; Fallon, Petkova, Keilp, & Britton, 2012; Johnson et al., 2018).

Although Lyme disease is not a rare disease, it is a research-disadvantaged disease. As Figure 7 reflects, the number of clinical studies for Lyme disease ranks well behind not only HIV/AIDS, but even behind leprosy—with its incidence of fewer than 200 cases per year (CDC, 2016, 2018b; CDC NCHHSTP, 2017; Goswami et al., 2013; Health Resources and Services Administration, 2020; Johnson et al., 2018).

Figure 7: Lyme Disease Ranking in Clinical Trials for Infectious Diseases



Source: Johnson et al., 2018; Derived from Goswami et al., 2013

NIH has funded three research grants for clinical trials for patients with persistent symptoms associated with Lyme disease—the last one over 15 years ago (Fallon et al., 2008; Klempner et al., 2001; Krupp et al., 2003). There are differing opinions regarding whether the trials were adequately designed and executed to provide definitive guidance to clinicians (Delong et al., 2012; Fallon et al., 2012; Klempner et al., 2013). For example, enrolled subjects do not necessarily reflect the larger patient populations with persistent manifestations of Lyme disease. While trial subjects had remained symptomatic for more than four years (Fallon et al., 2008; Klempner et al., 2001), many patients present for retreatment much sooner than that. Additionally, there is evidence that some of the designated changes for what constitutes a positive treatment effect were too great and thus unable to detect treatment effects that patients deemed meaningful (Delong et al., 2012; Fallon et al., 2012; Guyatt, Mills, & Elbourne, 2008). Detecting smaller changes often requires a much larger sample size.

Such trials typically require industry funding, but the pharmaceutical industry has generally not been interested in funding Lyme disease clinical treatment trials since treatment with generic antibiotics, as has become the norm for Lyme disease, does not provide adequate financial incentives. Two recent reports from the World Health Organization (WHO) demonstrate that, "research and development for antibiotics is primarily driven by small- or medium-sized enterprises with large pharmaceutical companies continuing to exit the field" (World Health Organization, 2019a, 2019b, 2020, January 17). These 2019 WHO reports on the lack of new antibiotics being developed was covered in a recent article in The Guardian: "The big pharmaceutical companies are not investing in antibiotic research because there is not a lucrative market for them" (Boseley, 2020).

Additionally, a 2019 IDSA news release states the following:

> While the numbers of antibiotics annually approved for marketing in the U.S. has increased following a decline in the previous decade, the authors found, the most recently approved drugs represent modifications to existing classes, rather than innovative approaches. With some momentum propelled by antibiotic incentives enacted in the last few years as well as by increased funding for NIAID and BARDA, the report finds that unmet needs persist, with far too few treatment options available for multi-drug resistant infections. At the same time, while larger pharmaceutical companies continue to leave the field, the small companies that are responsible for most of the antibiotic innovation are struggling to stay in business, the authors note. (Infectious Diseases Society of America, 2019, January 2)

The NIH trial findings were also inconsistent, with some demonstrating treatment success and others not. Hence, broad conclusions regarding antibiotic treatment cannot be drawn from the few NIH-funded randomized controlled trials. A review of the three NIH-funded studies describes the state of the science on treating patients with persistent symptoms associated with Lyme disease as follows:

> Based on the evidence cited above, one cannot conclude that repeated antibiotic therapy is ineffective in improving certain symptoms associated with post-treatment Lyme disease syndrome. Nor can it be concluded that repeated antibiotic therapy is robustly effective. One can conclude however that approximately 60 percent of patients with persistent post-treatment Lyme fatigue may

> experience meaningful but partial clinical improvement in fatigue with antibiotic retreatment. Guidelines for Lyme disease that address patients with chronic symptoms therefore need to clarify that the controlled trials of additional antibiotic therapy for post-treatment Lyme symptoms have revealed conflicting results, with some studies demonstrating efficacy and others not showing benefit to repeated treatment. (Fallon et al., 2012)

The inconsistent findings of the NIH-funded trials conducted thus far align with findings from a registry-based study of nearly 4,000 patients with persistent symptoms associated with Lyme disease, which showed treatment response heterogeneity using the type of subgroup analysis that small trials are inherently unable to detect (Johnson et al., 2018). (Other diseases such as Hepatitis C and tuberculosis use subgroup analysis to identify and target clinical treatment approaches toward treatment responders.) Hence, the state of the science for treating persistent Lyme disease patients is limited, unsettled, and emerging.

In the context of this uncertainty and the lack of research being conducted on the treatment of persistent Lyme disease, the question becomes: How do you treat patients who are sick today and cannot wait for tomorrow's research?

Evidence-based Medicine and Conflicting Guidelines in Lyme Disease

Evidence-based medicine is defined as "the integration of best research evidence with clinical expertise and patient values" (Sackett, Strauss, Richardson, Rosenberg, & Haynes, 2000). The National Academy of Medicine (NAM) reaffirms the role of clinical judgment and patient preferences, as does the widely used evidence assessment scheme, GRADE (Guyatt et al., 2008; Institute of Medicine, 2011). The difficulty of developing clinical treatment guidelines when the evidence base is limited, emerging, and unsettled is recognized by NAM:

> The committee is well aware that for many aspects of health care, scant or no evidence of either effectiveness or ineffectiveness exists. . . . It is clearly not possible to base all care on sound scientific evidence, and certainly not exclusively on randomized controlled trials, which narrowly define study populations and exclude or control for factors that are inevitably relevant in real-world care settings. (Institute of Medicine, 2001)

NAM recommendations on creating trustworthy guidelines note that guidelines developed "where high quality evidence is lacking or even nonexistent" should avoid dictating a one-size-fits-all approach and, instead, reflect the dearth of evidence and thus permit individualized care. In Lyme disease, there is no optimal diagnostic or treatment pathway. Instead, two sets of divergent diagnostic and treatment guidelines have been published in peer-reviewed journals: one promulgated by IDSA and the other developed by the International Lyme and Associated Diseases Society (ILADS) (Cameron et al., 2014; Wormser et al., 2006). The ILADS guidelines meet the rigorous standards imposed by NAM for guidelines development, including the use of the GRADE evidence assessment scheme, while IDSA is in the process of developing guidelines aimed toward meeting these criteria.

Conflicting guidelines are not uncommon. NAM notes that at least 25 conditions have conflicting guidelines—most often arising when evidence is weak, organizations use different assessment schemes, or when evidence developers place different values on the benefits and harms of intervention (Institute of Medicine, 2011). Given these distinctions, the various sectors involved tend to subscribe to one set of guidelines or the other. So, while Federal agencies like CDC, medical boards, and insurers reference the IDSA guidelines, clinicians that treat the majority of patients with persistent symptoms associated with Lyme disease tend to follow the ILADS guidelines.

It is important to note here that for patients with persistent symptoms associated with Lyme disease, almost all (of those who have been, or who are being, actively treated for their symptoms) select practitioners who follow the guidelines of ILADS. Very few (6%) of these same patients report being treated by infectious disease physicians who follow only the IDSA guidelines (Johnson et al., 2018). Based on our experience, we believe that this is largely driven by a patient need for more treatment options and more clinical innovation in that treatment, along with a desire by the patient to be actively involved in their plan of care.

There are many differences between the two sets of guidelines. The IDSA guidelines provide very specific diagnostic criteria and limited treatment options, which result in a uniform approach to patient care; the ILADS diagnostic and treatment guidelines, on the other hand, are less restrictive and uniform in approach, recognizing the differences in individual patient presentation and response to various treatment options, and placing an emphasis on the exercise of clinical judgment and shared medical decision-making based on the individual patient and his or her experience of the illness.

Although IDSA is aware that there are two standards of diagnosis and care for patients with Lyme disease, their treatment guidelines do not disclose this fact, and many patients and clinicians may not be aware that another diagnostic and treatment approach exists. In contrast, ILADS guidelines advise physicians to 1) inform their patients that IDSA guidelines recommend a different diagnostic and treatment approach, and 2) utilize informed and shared medical decision-making with their patients (Cameron et al., 2014; Wormser et al., 2006). By limiting the criteria for the diagnosis of Lyme disease and the options for subsequent treatment, the more uniform and prescriptive approach of the IDSA diagnostic and treatment guidelines certainly allows for greater and more simplified data collection of patients diagnosed and treated under those guidelines.

However, the very uniformity of the IDSA guidelines that is a strength in this regard may also be a weakness in that such an approach leaves little room for individual practitioner clinical judgment. That clinical judgment must be based on the practitioner's own clinical experience, and/or on the clinical experience of other practitioners who have successfully diagnosed and treated a significant number of patients with acute Lyme disease, as well as patients with persistent symptoms associated with Lyme disease. These patient case histories, clinical experiences, and successful outcomes need to be shared with other clinicians who are also attempting to accurately diagnose and effectively treat these patients, for the benefit of all patients, and must be considered when establishing clinical guidelines such as these.

Additionally, while the ILADS guidelines use a patient-oriented approach to clinical outcomes (that is, outcomes that are directly related to the patient's experience of their illness: mortality, morbidity, symptom reduction, quality of life, and cost of illness), the IDSA guidelines emphasize a disease-oriented outcome approach. Disease-oriented outcomes are surrogates for the patient-oriented ones and rely on pathophysiologic markers, laboratory tests, and physical exam findings (Ebell et al., 2004), and not on the patient's experience of illness.

The key differences between the two sets of guidelines are shown in Table 5.

Table 5: Comparison of Conflicting Guidelines in Lyme Disease

IDSA Guidelines (Wormser et al., 2006)	ILADS Guidelines (Cameron, Johnson, & Maloney, 2014)
Disease-oriented diagnosis (Ebell et al., 2004)	Clinical diagnosis
Erythema migrans rash alone or physical findings consistent with Lyme disease accompanied by positive two-tier test results	Clinical signs and symptoms with lab tests supportive of the clinical manifestations
Short-term treatment protocols	Longer treatments may be appropriate
No persisting infection (do not treat)	Persisting infection may be present
Retreatment of late-stage presentations: 2x (up to 3x) for Lyme arthritis; only 1x for other late-stage presentations; limited in nature	Retreatment with emphasis on shared medical decision-making and patient education, regardless of type of late-stage presentation and severity of illness
Disease-oriented outcomes (Ebell et al., 2004)	Patient-oriented outcomes
Clinical judgment emphasis limited	Clinical judgment emphasis
Shared medical decision-making is limited or precluded in order to present a more uniform approach to treatment, and the individual patient experience of illness is generally not a factor; No acknowledgment of ILADS guidelines and no recommendation for disclosure to patient; Retreatment, except for Lyme arthritis, is strongly discouraged	Shared medical decision-making is encouraged with patient/physician shared decisions focused on individual patient values, as well as individual patient details and his or her experience of illness; Acknowledgment of IDSA guidelines and recommendation for full disclosure to patient; Retreatment with emphasis on shared medical decision-making coupled with patient education

Shared Medical Decision-Making Is Appropriate Especially When Evidence Is Unsettled

The diagnosis and treatment of Lyme disease and other tick-borne diseases and conditions may entail that physicians discuss all available diagnostic and treatment regimens with patients as part of shared decision-making. When two divergent treatment approaches exist for a disease, the principle of shared medical decision-making indicates that clinicians should inform the patient of the existing evidence base and any associated uncertainties and engage in a dialogue with the patient that considers both the clinician's judgment as well as the patient's values. Shared decision-making assumes greater importance when the evidence base is weak and considerable heterogeneity exists among patients, making a one-size-fits-all approach inappropriate (Atkins, Siegel, & Slutsky, 2005).

According to a 2013 article in the peer-reviewed *Journal of Comparative Effectiveness Research*, the term "shared decision-making" in health care might have appeared in the medical literature over 30 years ago, but its underlying model of mutual participation was first described in 1956 (Gionfriddo et al., 2013). The mutual participation model represented a departure from medical practice solely as a clinician-driven activity and introduced it as a give-and-take relationship, based on equality and respect. Even from its earliest stages, this model was felt to be particularly useful in the management of chronic conditions. This recognition that behavioral, psychosocial, and lifestyle interventions, in the hands of patients, could affect health beyond the effect of biomedical interventions, furthered the interest in engaging patients in health care. It was in this context of changing ethical and clinical thought that shared decision-making began to develop an identity: In 1982, a Presidential Commission Report concluded that "shared decision-making is the appropriate ideal for patient–professional relationships." At first, the practice of this 'appropriate ideal' manifested primitively as informed consent and patient education. It was not until the late 1990s that Charles et al. [1997] provided a formal framework for the application of SDM in clinical practice" (Gionfriddo et al., 2013).

And as an article in the May 2020 *AMA Journal of Ethics* noted, "Even if SDM [shared decision making] is not the best term or clearest descriptor for the process by which clinicians and patients work together to arrive at the patient's decisions, SDM does represent a significant evolution in medical culture such that patient autonomy is key and clinicians are expected to consider and, within appropriate limits, abide by their patients' preferences" (Childress & Childress, 2020).

Although many conditions that involve trade-offs use shared decision-making approaches, perhaps the most well-known examples of shared decision-making are those involving breast cancer and prostate cancer treatment options, where patients are provided with information about available treatment options and make decisions in consultation with the practitioners (Martinez, Kurian, Hawley, & Jagsi, 2015; Mulley & Barry, 1998). As NAM explains, shared medical decision-making has the most value when evidence is uncertain: "Informed choice under uncertainty is an ideal to strive for, especially because it enhances the exercise of the patient's right of self-determination, which is a cornerstone of medical ethics" (Institute of Medicine, 2011). This is because patients alone must live with the

consequences of the medical intervention taken or declined (Barry & Edgman-Levitan, 2012). Because of this, patients are sometimes referred to as the "ultimate stakeholder" (deBronkart, 2013).

The Office of the National Coordinator for Health Information Technology explains the necessity for shared medical decision-making in the context of individual preferences and treatment response variation:

- In many situations, there is no single 'right' healthcare decision because choices about treatment, medical tests, and health issues come with pros and cons. Shared decision-making is especially important in these types of situations:
- When there is more than one reasonable option, such as for screening or a treatment decision;
- When no one option has a clear advantage; and
- When the possible benefits and harms of each option affect patients differently (HealthIT.gov, 2013).

Shared medical decision-making is embraced in the *Patient Protection and Affordable Care Act* of the U.S. Federal Government as well as:

- The Agency for Healthcare Research and Quality (AHRQ, 2018);
- The Centers for Medicare & Medicaid Services (Merchant, Dickert, & Howard, 2018);
- HealthIT.gov (HealthIT.gov, 2013);
- National Quality Forum (National Quality Partners, 2017); and
- The Patient Centered Outcomes Research Institute (PCORI, 2019).

Shared medical decision-making would provide patients with the knowledge essential to navigate and more quickly obtain prompt diagnosis and treatment to improve health outcomes. However, it is impossible for shared decision-making or informed choice to occur unless all of the stakeholders—patient, clinician, clinical institution or hospital, and insurance company—are aware that divergent approaches to diagnosis and treatment exist.

As healthcare consumers, patients are best served when they are made aware of their treatment options and can actively participate in selecting a treatment program that meets their individual needs and goals. This is the essence of shared decision-making, which is an especially useful approach when the optimum therapy has not been established and the risks and benefits of various treatments affect individual patients differently.

Recommendation 7.2: Fund and support a directive for CDC (or other appropriate HHS OPDIV or agency) to develop (either directly or through an approved federal contract) a multi-leveled and nationwide curriculum on Lyme disease for clinicians-in-training as well as continuing medical education modules to increase the pool of qualified and practicing clinicians. Provide funding for the U.S. military to participate in this nationwide training and education on Lyme disease and other tick-borne diseases and conditions. This curriculum should be introduced and encouraged at the State level. The final curriculum shall incorporate feedback from patients, clinicians, and research scientists with expertise/experience that represents diverse scientific and clinical experiences on the full spectrum of Lyme disease and other tick-borne diseases/conditions.

Available Clinician Training Is Limited

Sufficient education and training of clinicians is a major gap for all tick-borne diseases of public health importance. Lack of awareness is one of the primary reasons that patients are undiagnosed or misdiagnosed. At present, only a few medical school hours are dedicated to tick-borne illnesses, and there are no post-graduate training requirements for primary care providers. For example, at the Uniformed Services University of the Health Sciences, tick-borne diseases are generally covered in one-hour lectures that include discussions of non-tick-borne diseases as well. Subject matter experts fulfill lecture requests via a variety of different university departments. Opportunities for continuing medical education on tick-borne diseases for both civilian and military practitioners in the military health system (TRICARE), which impacts active duty personnel, retirees, and their beneficiaries, as well as for practitioners in the VA healthcare system, which serves any eligible military Veteran, is significantly limited if not totally nonexistent (Training, Education, Access to Care & Reimbursement Working Group Subcommittee, 2019).

Medical school curricula must prepare students with a wide range of materials over a short period of time. The magnitude and significance of tick-borne diseases is often underappreciated and may be an obstacle to commanding the time and resources necessary to develop comprehensive educational curricula. The rapidly emerging science and the introduction of new tick species and pathogens are other obstacles to clinician education as they will necessitate frequent revisions of educational curricula.

During residency, physicians-in-training often have substantial and hectic workloads. For infections that vary regionally, physicians training in one part of the country may not be able to obtain clinical experiences and exposure to patients with tick-borne diseases specific to other areas that might optimally prepare them for future practice in regions where they might need to have this specific knowledge. Clinicians in practice are also very busy and often have little time to gather the necessary and specific clinical information and formulate a plan of care for the various tick-borne diseases, which may contribute to missing an important diagnosis. Those on the front line of care (for example, primary care and emergency medicine physicians and advanced practice providers, such as nurse practitioners and physician assistants) often deal with a great variety of medical problems, and may not readily

distinguish tick-borne diseases and conditions from the variety of alternative causes of fever, rash, and headache. Strategies to enhance clinician education, both initial and ongoing, should be formulated in a way that accounts for these obstacles.

Education and awareness of Lyme disease and the other tick-borne diseases discussed in this chapter will help prevent disease and improve diagnosis and treatment of patients. The lack of medical education hours devoted to tick-borne disease diagnosis and treatment is made most notable by the fact that these hours are woefully out of proportion to the significance of these diseases, especially Lyme disease, as evidenced by the number of new cases reported every year in the U.S. and coupled with the staggering number of individuals who have not only been diagnosed with these diseases, but who have also been adversely impacted (often severely) by Lyme disease and other tick-borne diseases. At present, only a few medical school hours are dedicated to tick-borne illnesses, and there are no post-graduate training requirements for primary care providers. The limited recognition of the magnitude and the potential for significant health and quality of life impairments due to Lyme disease and other tick-borne diseases, as well as the limited recognition of the emerging science, particularly with regard to the potential for persistent manifestations associated with Lyme disease, may reduce the willingness to develop comprehensive educational programs. Finally, the incorporation of feedback from patients, clinicians, and research scientists with the critical expertise and experience that represents diverse scientific and clinical experiences of Lyme disease and other tick-borne diseases will be essential to the development and promulgation of a robust nationwide training and education program on Lyme disease and other tick-borne diseases.

Recommendation 7.3: Fund efforts across the U.S. to expand/require medical education to inform emergency, primary care, and other healthcare providers and to raise clinician and public awareness of rickettsial (including Rocky Mountain spotted fever), ehrlichial, and anaplasmal diseases.

Similar to our discussion for Recommendation 7.2 regarding Lyme disease and other tick-borne diseases in general, education and awareness of life-threatening rickettsial, ehrlichial, and anaplasmal diseases will not only help prevent disease and improve diagnosis and treatment of patients, but it will reduce morbidity and mortality caused by these particular diseases. Clinician education should focus on symptomology, the presence or absence of rashes and eschars, diagnostic limitations, and appropriate treatment options, especially for children.

As we have already determined for Lyme disease and other tick-borne diseases in general, the lack of medical education hours devoted to these life-threatening tick-borne diseases and their diagnosis and treatment is made most notable by the fact that these hours are woefully out of proportion to

the significance of these diseases, as evidenced by the number of new cases reported every year in the U.S., and which continues to rise dramatically. At present, only a few medical school hours are dedicated to tick-borne illnesses in general, and there are no post-graduate training requirements for primary care providers.

Recommendation 7.4: Fund efforts across the U.S. to expand/require medical education to inform emergency, primary care, and other healthcare providers and to raise clinician and public awareness of babesiosis, tick-borne relapsing fever, emerging tick-borne viral infections, and other low-incidence tick-borne diseases.

Given their prevalence and the serious adverse impact that babesiosis (CDC, 2018a) and tick-borne relapsing fever have on patients, we believe that increased and focused education and awareness efforts especially for these two diseases (as well as for efforts aimed at increasing awareness and education on emerging tick-borne viral infections and other low-incidence tick-borne diseases), will help prevent disease and improve diagnosis and treatment of patients. If healthcare providers do not know about these uncommon diseases, they will never consider them in their diagnoses nor order tests for them.

Education should include epidemiology, natural history, signs and symptoms, preferred specimens and volumes for collection, recently licensed tests to screen for *Babesia* species in blood donors (U.S. Food and Drug Administration, 2019), laboratory shipping requirements, and treatment options. Prevention education should target high-risk groups (for example, hunters, anglers, ranchers, landscaping workers), especially in regions where transmission is known to occur.

Recommendation 7.5: Generate broad awareness of Alpha-gal Syndrome through the following two mechanisms:

- Provide funding/support/resources necessary to create a National Tick-Borne Alpha-gal Syndrome Alert that is focused on awareness, prevention, and education regarding tick associated Alpha-gal Syndrome and that targets key stakeholder groups.
- Label foods/beverages, medications and medical products, cosmetics, etc. containing mammalian-derived components for the safety of consumers with Alpha-gal Syndrome.

In a recent survey of 131 patients with AGS, the top two overwhelming concerns were the lack of healthcare provider knowledge about AGS (89%) and the need for ingredient labeling on food and pharmaceuticals (79%) (Flaherty et al., 2017). Platt and Carrison (2019) also reported a lack of knowledge about AGS across groups of pharmacists, public health practitioners, product manufacturers (household products, cosmetics, medical and dental devices, and pharmaceuticals—both over-the-counter and prescription), schools, employers, policymakers, legal counsel, and the general public. Raised awareness and education represents a critical need for patients with AGS and their families, but in particular for providers across the healthcare system, including but not limited to emergency medical

transportation staff members who are called in for emergencies and unwittingly administer IV fluid with gelatin, general practitioners taking care of patients who present with unexplained hives, and dentists whose patients react badly to topical numbing gels.

Patients with AGS are often left to their own devices for education and ongoing support. However, providing proper education and guidance after diagnosis is crucial to a patient's safety and successful management of AGS. To better support patients with AGS, their families, and others who provide services to them, accurate and up-to-date educational materials on AGS are needed. Materials should address prevention, diagnosis, treatment, and ongoing supportive care. Increased education and awareness will reduce harm from unnecessary exposure and unnecessary medical costs (for example, emergency room visits) caused by misdiagnosis, inappropriate prescriptions, and unnecessary hospitalizations (Crow, Samples, & Purser, 2019; Florin-Dan Popescu, Cristea, Floriana-elvira Ionica, & Vieru, 2019).

As with management for any food allergy, AGS management is based on allergen avoidance. For patients with AGS, however, this tenet of self-protection is made difficult by the lack of adequate labeling for mammalian-derived sources in foods, medications, and vaccines. Supporting healthcare professionals and patients with alpha-gal-free ingredient labeling will reduce exposure and costs, including direct costs related to emergency room visits and treatments, and indirect costs from lost work and school productivity.

Minority Response 1

The Tick-Borne Diseases Working Group (hereafter, "Working Group") was established with the charge of enabling different viewpoints to be heard. While the goal of the Working Group is to reach mutual agreement on the recommendations and chapter content in each report, group consensus is not always achieved. In the spirit of the Working Group's mission and in service to the patients, physicians, and others seeking to understand the current state of science in tick-borne diseases, we offer the following opinion to ensure that a diversity of perspectives is presented and the balance to which the Working Group aspires is achieved.

Tick-Borne Disease Working Group rules require individual members to vote in the minority on a chapter or a section of a chapter in order to write a minority response. Chapter 7 passed by an 8 to 6 vote. Despite its passage, several members of the majority expressed concerns about its content, and openly encouraged dissenting members to submit minority responses to address those concerns. Representatives from NIH, CDC, and FDA independently voted against the chapter so that important information could be included, and we explain our prevailing concerns here.

First, we wish to make clear that we recognize and are greatly concerned by the suffering and disability reported by the patient community. The first NIH-funded clinical trial on long-term antibiotics made it clear that those enrolled in the study had significant disability (Klempner et al., 2001), and the public comments received by the Working Group clearly reflect a community in need. We fully support the recommendations listed in this chapter, and in no way do we suggest that clinician and public education and access to care are not important elements of this report.

Rather, our concerns are with some key omissions and misrepresentations in portions of this chapter, in particular some of the Lyme disease information contained within the background section and the rationale provided for Recommendation 7.1. Those concerns, and our inability to come to a compromise on the language in the text, resulted in our reluctance to accept the chapter as written. Much of the background appears to be unrelated to the recommendations. In addition, we have concerns about a lack of balance and the presence of inaccuracies within the text. Specifically, this chapter presents an incomplete assessment of clinical treatment trials, a misrepresentation of the IDSA treatment guidelines, and the conflation of inadequately defined disease registries with cohorts that have been established using objective diagnostic criteria.

First, the chapter calls into question whether several NIH-supported clinical trials on extended antibiotic treatment were "adequately designed and executed," and several times mentions the inconsistency of results. While the chapter authors have rightly indicated that some individuals have challenged a subset of the results, the authors focus solely on that side of the argument. In fact, the published outcomes of those trials consistently demonstrated no sustained benefit from extended antibiotic therapy and an unacceptable level of adverse events. The challenges have focused on secondary endpoints, isolated subsets, and transient benefits and do not change the overall conclusions of the trials. This is not made clear in the chapter, nor are the results of a critical reassessment of those trials that found no justification for changing the original conclusions (Klempner et al., 2013). Multiple groups

have published on the strength of the trial results (Feder et al., 2007; Lantos, 2015; Melia & Auwaerter, 2016). In addition, the authors of a recent clinical trial conducted in Europe acknowledged the validity of those earlier results. They nevertheless conducted an additional placebo-controlled trial comparing different antibiotic regimens for Lyme disease and reached the same conclusion: There was no benefit from extended antibiotic therapy (Berende et al., 2016; Berende et al., 2019). None of this information is presented in the chapter.

It is important to highlight concerns about study design or outcomes, and it remains clear that differences exist in interpreting the published clinical trial data. By highlighting only one side of the argument, however, this chapter presents an incomplete assessment of current scientific thought and ignores the substantial data that run contrary to the authors' position.

With further regard to treatment, the differences between IDSA and ILADS guidelines were regular topics of robust discussion within the Working Group. Appropriately, both are mentioned in this report. However, the IDSA treatment guidelines are misrepresented. Contrary to this chapter, IDSA supports both patient input and the physician's individual clinical experience in guiding treatment decisions. It is unclear what is meant by "disease-oriented" versus "patient-oriented" outcomes, or by "disease-oriented" versus clinical diagnosis, but it is incorrect to suggest that IDSA recommendations are not focused on patients' health. The differences between the two sets of guidelines lie not in their positions on the role of patient and practitioner in determining course of treatment. Rather, they lie in the type and strength of evidence accepted by the guideline authors for determining potential avenues of effective therapy.

A third issue with this chapter lies in the source of data used to describe the Lyme disease patient experience. Much of the information provided is based on data from Lyme disease patient registries and surveys. Patient registries can indeed be valuable tools for studying disease. As was acknowledged during the Working Group proceedings, however, there is no current case definition for chronic Lyme disease, a condition that is strongly represented within the patient community. Without a consensus case definition and objective diagnostic criteria—and given the broad range of symptoms that have been attributed by some to Lyme disease—there is no way to confirm whether individual registrants are suffering from Lyme disease or from one of many alternative conditions. This is especially critical given evidence for Lyme disease misdiagnosis (Kobayashi et al., 2019). Until these issues can be addressed, it will be difficult to glean useful information on the Lyme disease patient experience garnered from these surveys and registries.

In short, many people are suffering from a range of sometimes debilitating symptoms attributed to Lyme disease. Disagreement continues to revolve around the causes of those symptoms and the best way to prevent, diagnose, and treat them. Regardless of that disagreement, all sides of the debate acknowledge the legitimate suffering experienced by affected patients. As such, the goal of all of us is to provide the best possible research and care in support of those in medical need.

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Minority Response 2

A great portion of this chapter is devoted to statements that are not supported by scientific evidence, but are promulgated by activists whose focus is on what they term persistent Lyme disease. This minority response addresses these inaccurate statements. To be clear, many people who report that they have persistent or chronic Lyme disease truly are suffering and desperately need relief from their debilitating symptoms. Unfortunately, many have decided, without appropriate evidence, that their suffering is caused by Lyme disease.

For example, the five bullet points in this chapter related to difficulty with access to care are based on a survey of patients with self-identified chronic Lyme disease. The accuracy of this diagnosis is highly questionable. More than half of the patients in the survey reside in the southern and western states, which account for a tiny fraction of all reported cases of Lyme disease. A large proportion of patients in the sample also claimed to have co-infections with microorganisms that are not transmitted by *Ixodes* ticks as well as other infections that are not transmitted by ticks at all. More than half of the patients claimed to have *Babesia* co-infections despite residing in geographic areas where there has never been a confirmed case of babesiosis. Indeed, many live in states in which locally acquired Lyme disease or even the finding of *Borrelia burgdorferi* in ticks is either rare or nonexistent.

Other patients who were not included in the above-referenced survey had acute Lyme disease, were treated, and continue to have debilitating symptoms. The evidence that these symptoms are due to active infection with *Borrelia* is either weak or non-existent. Indeed, multiple different studies from different major medical centers have found that when patients alleged to have chronic Lyme disease are evaluated by experts, a majority have no evidence of having Lyme disease either at the time of evaluation or at any time in the past. Moreover, contrary to what is implied in this chapter, there have been numerous well-designed and well-conducted randomized clinical trials (some sponsored by the NIH) which have found that treatment of such patients with additional prolonged courses of antibiotics provides no meaningful benefit and may result in serious adverse side effects and substantial costs. Single-minded focus on curing a hypothetical infection with prolonged courses of antibiotics will not alleviate these patients' problems.

Much of the material about Lyme disease in this chapter is not related to the actual recommendations in this chapter that have been approved by the Tick-Borne Diseases Working Group. If this material was designed to dictate the content to be included in government websites, this was not the intention of the Tick-Borne Diseases Working Group. There is a long section in this chapter on shared decision-making that delineates ethical principles that are already currently solidly embedded in both medical education and medical practice. While we certainly support shared decision-making, unfortunately the implication of much of what is written about it in this chapter implies that shared decision-making means that the physician should do whatever the patient wants, even if it means offering treatments, such as prolonged and repeated courses of antibiotics, that clearly have been demonstrated to be no more effective than placebo in treating these symptoms but that are associated with risks of adverse effects as well as with substantial financial costs. This clearly is inappropriate.

There is considerable material in this chapter that suggests that data about both the causes and the optimal treatment of patients with persistent symptoms attributed to Lyme disease is limited, emerging, and unsettled. It is also stated or implied that there are opposing and equally well-supported viewpoints about this issue represented by the guidelines of the Infectious Diseases Society of America (IDSA) and by those of the International Lyme and Associated Diseases Society (ILADS). Table 5, in which the guidelines are compared, characterizes those of the IDSA as "research-oriented" diagnosis and outcomes and "limited" clinical judgment and decision-making, while ILADS guidelines are characterized as favoring "clinical" diagnosis, "patient-oriented" outcomes, and clinical judgment and decision-making that is not limited. It also states that the IDSA guidelines leave "…little room for individual practitioner clinical judgment that is based on the practitioner's own clinical experience and/or on the clinical experience of other practitioners…" Nothing could be further from the truth. The IDSA guidelines clearly state that "it is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances" (Wormser et al., 2016). IDSA recommendations for diagnosis and treatment are evidence-based, while those of ILADS are not. Furthermore, although not acknowledged in this report, ILADS policies are gross outliers. A survey of family practitioners in Connecticut, a state in which Lyme disease is highly endemic, found that only 2% of them diagnosed and treated chronic Lyme disease (Johnson & Feder, 2010). Moreover, numerous other professional organizations in the United States (e.g., the American College of Rheumatology and the American Academy of Neurology) and in at least a dozen different European countries independently developed guidelines based on the scientific evidence that are very similar to those of the IDSA. The Health Protection Agency of the United Kingdom arranged for an independent review of the ILADS guidelines which concluded that they were "...poorly constructed and do not provide a scientifically sound evidence-based approach to the diagnosis and care of patients with Lyme borreliosis" (Health Protection Agency of the United Kingdom, 2010). To characterize guidelines that use evidence from valid scientific research to assist physicians in developing an effective approach to diagnose and to treat patients with Lyme disease as "research oriented" as opposed to "patient oriented" is inappropriate and is a false dichotomy.

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Minority Response 3

While the recommendations in Chapter 7 have been approved by the Working Group, some parts of the chapter content expand into subject matter that is not associated with the recommendations or is not sufficiently supported by literature. For example, while the need for new antibiotics is appreciated, this position was not pertinent to Recommendation 7.1. Likewise, in Table 5, which provides a comparison of Lyme Disease treatment guidelines, the references cited for outcomes, clinical judgment, and shared medical decision-making do not support the distinctions presented.

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Chapter 8

Epidemiology and Surveillance

Recommendations at a Glance: Epidemiology and Surveillance

Recommendation 8.1: Fund prospective studies of acute febrile illnesses to assess the burden of tick-borne diseases, including rickettsial, ehrlichial, and anaplasmal pathogens.

Recommendation 8.2: Recommend that CDC work with Council of State and Territorial Epidemiologists (CSTE) to streamline the surveillance process and to reduce the burden on both clinicians and public health departments by permitting direct laboratory reporting of positive cases.

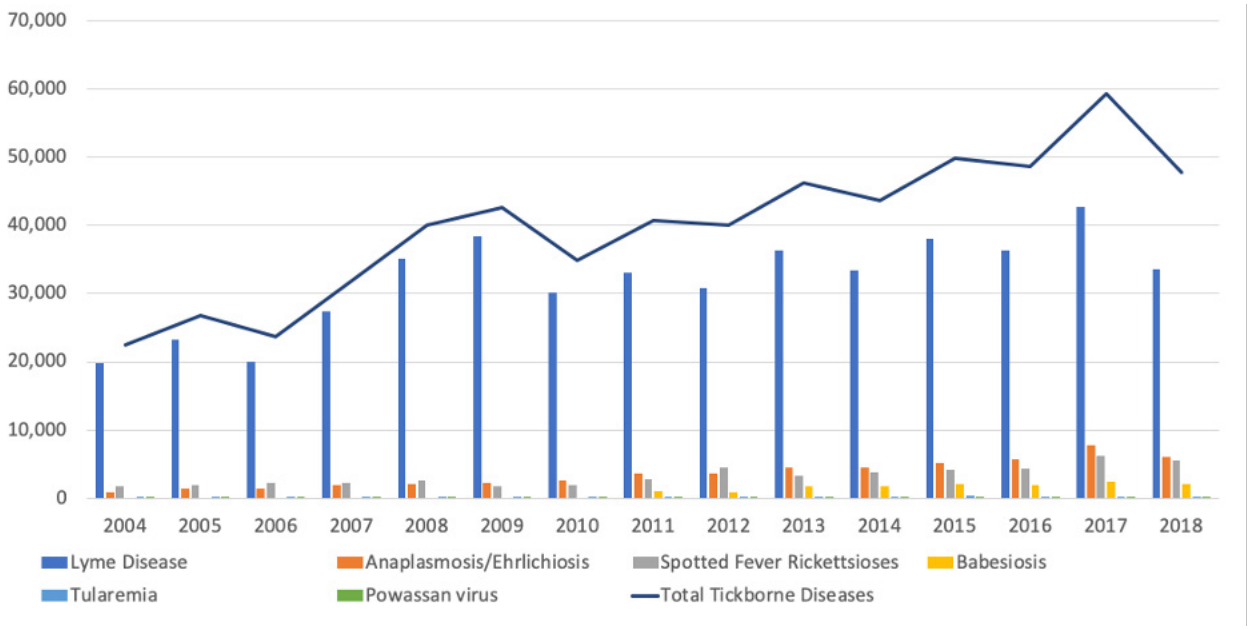
Recommendation 8.3: Further evaluation of non-tick bite transmission of Lyme disease, for example maternal-fetal transmission.

Background

The number of tick-borne diseases reported each year has been increasing steadily over the last two decades (Figure 8). Tick-borne diseases currently account for almost 80 percent of all nationally notifiable vector-borne diseases reported to the Centers for Disease Control and Prevention (CDC) each year (Table 6). In 2017, 59,349 cases of tick-borne diseases were reported to CDC, a 22 percent increase over reported cases in 2016 (CDC, 2019d). This count was the highest number of tick-borne disease cases ever reported in a single year in the United States and included the following case numbers:

- Lyme disease - 42,743
- Anaplasmosis and ehrlichiosis - 7,718
- Spotted fever rickettsiosis - 6,248
- Babesiosis - 2,368
- Tularemia - 239
- Powassan virus - 33

Figure 8: Total Reported Tick-borne Disease Cases, 2004-2018



Source: Centers for Disease Control and Prevention

Table 6: Reported Tick-borne Disease Cases and All Vector-Borne Diseases Cases, 2004-2018

Tick-borne Diseases	Year															
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Lyme Disease	19,804	23,305	19,931	27,444	35,198	38,468	30,158	33,097	30,831	36,307	33,461	38,069	36,429	42,743	33,666	**478,911**
Anaplasmosis / Ehrlichiosis	875	1,404	1,455	1,999	2,107	2,267	2,615	3,586	3,725	4,551	4,488	5,137	5,750	7,718	6,123	**53,800**
Spotted Fever Rickettsiosis	1,713	1,936	2,288	2,221	2,563	1,185	1,985	2,802	4,470	3,359	3,757	4,198	4,269	6,248	5,544	**49,168**
Babesiosis	N	N	N	N	N	N	N	1,128	937	1,796	1,760	2,100	1,910	2,368	2,160	**14,159**
Tularemia	134	154	95	137	123	93	124	166	149	203	180	314	230	239	229	**2,570**
Powassan virus	1	1	1	7	2	6	8	16	7	15	8	7	22	33	21	**155**
Subtotal Tick-borne Diseases	22,527	26,800	23,770	31,808	39,993	42,649	34,890	40,795	40,119	46,231	43,654	49,825	48,610	59,349	47,743	**598,763**
Total All Reported Vector-Borne Diseases*	**27,385**	**33,874**	**30,484**	**41,401**	**43,803**	**47,655**	**49,395**	**45,175**	**54,110**	**61,142**	**56,374**	**55,644**	**96,071**	**66,862**	**51,482**	**760,828**

***Notifiable vector-borne diseases; anaplasmosis/ehrlichiosis infections, babesiosis, California serogroup virus diseases, chikungunya virus disease, dengue virus infections, eastern equine encephalitis virus disease, Lyme disease, malaria, plague, Powassan virus disease, spotted fever rickettsiosis, St. Louis encephalitis virus disease, tularemia, western equine encephalitis virus disease, yellow fever, zika virus infection and disease

Source: National Notifiable Disease Surveillance System, Centers for Disease Control and Prevention

Under-reporting is a common phenomenon for most high-incidence diseases. For Lyme disease, the actual number of annual cases has been estimated at 8 to12 times higher than the number of reported cases (Hinckley et al., 2014; Nelson et al., 2015). Under-reporting occurs for anaplasmosis, ehrlichiosis, and rickettsiosis as well.

The Tick-Borne Disease Working Group 2018 Report to Congress included three noteworthy recommendations that relate to surveillance practices. These specifically addressed the need for the following:

- Novel quantitative approaches that could complement traditional national surveillance activities;
- Systematic tick surveillance activities to better understand geographic expansion of Lyme disease distribution and risk; and
- Systematic studies to identify and characterize novel tick-borne pathogens.

Since that report was issued, progress has been made in each of these areas. For example, CDC has explored with the state health departments the feasibility of using insurance claims data and electronic health records, in addition to passive disease surveillance, for the purpose of describing burden and trends, monitoring distribution and spread, and refining our knowledge of the disease and the pathogen. Additionally, a national tick surveillance system has been established between the CDC and state health departments, that provides for annual posting of tick and pathogen distribution data based on active tick collection efforts (CDC, 2020h). A metagenomics-based collaborative study of patients with illness associated with a tick bite has now obtained specimens from 30,000 patients enrolled at the Mayo Clinic. Specimens are currently being evaluated, but preliminary analysis has already resulted in identification of a novel *Borrelia* species not previously observed in humans (Kingry et al., 2018).

Consequently, significant progress has been made. The recommendations in this chapter report build upon the recommendations of the Tick-Borne Disease Working Group 2018 Report to Congress, addressing additional needs related to tick-borne disease epidemiology and surveillance.

Major Challenges and Issues

The numbers of reported tick-borne disease cases in the United States more than doubled from 2004 to 2016 (Rosenberg et al., 2018). Similarly, the number of counties in which the most important tick vector, *Ixodes scapularis*, is now established has more than doubled in the last 20 years (R. J. Eisen, Eisen, & Beard, 2016). The prevention and control of vector-borne diseases in general and of tick-borne diseases specifically is hampered by numerous obstacles, including the lack of both vaccines and effective vector control tools, as well as insufficient technical capacities in public health entomology at Federal, state, and local levels (Beard, Visser, & Peterson, 2019). In short, there are more disease cases, more pathogens, and more people at risk now than ever before.

Another important challenge is the availability to healthcare providers of rapid and accurate diagnostic tests for many tick-borne disease agents (Fang et al., 2017). Currently, there are no rapid point-of-care diagnostic testing methods to ensure the accurate diagnosis of any of the rickettsial diseases early in the illness. The serologic detection of anti-rickettsial antibodies is the mainstay of laboratory testing, but detectable antibodies are generally not present in the first week of illness when patients first seek evaluation (Biggs et al., 2016). Several hurdles exist that prevent accurate diagnosis and treatment of

rickettsial diseases: 1) There is no generally available test for diagnosis of acute infection; 2) knowledge and awareness of laboratory diagnostics and appropriate treatment by many physicians are lacking; 3) diagnosis based on clinical manifestations early in the course of illness is very difficult; and 4) only a limited number of antibiotics are effective (G.S. Marshall et al., 2003). Similarly, there is a need for new diagnostic tests that directly detect the presence of the bacteria that cause Lyme disease. The results of current antibody-based diagnostic tests may not yet be positive in the early stages of illness, before the antibody response is detectable. Likewise, antibody test results may remain positive for many years in individuals who have had previous Lyme disease but who no longer have active infection by currently available tests. It has also been shown that they may not be positive in active infection when the antibody and antigen may form complexes. There are no commercial tests available to test for complexed antibodies (Schutzer, Coyle, Reid, & Holland, 1999). The need for effective recognition, diagnosis, treatment, and prevention of all tick-borne diseases is critical given the absence of any approved vaccine to prevent these infections in humans.

Surveillance for tick-borne diseases continues to be challenging. Decreased financial support for all vector-borne diseases has eroded the ability of state and local public health officials to accurately monitor human disease incidence and to monitor changes in vector populations that can predict increased risk (Hadler et al., 2014). Traditional public health and disease surveillance is a passive process whereby healthcare providers and laboratories report positive diagnoses or laboratory tests to public health agencies. Passive surveillance systems work best for diseases that are rare, involve hospitalized patients, or for which there are definitive laboratory diagnostic tests. Passive systems are less effective for diseases that are typically diagnosed in outpatient settings and for which both laboratory tests results and corroborating clinical data are required (Cartter, Lynfield, Feldman, Hook, & Hinckley, 2018; Schwartz, Hinckley, Mead, Hook, & Kugeler, 2017), such as Lyme disease.

Because national surveillance for spotted fever rickettsiosis is based exclusively on passive reporting of cases that are largely confirmed by non-specific serologic tests that often detect background seroprevalence rather than confirm an active disease, these data are unlikely to accurately describe the magnitude of these diseases or to identify the specific agent responsible for the actual illness. In this context, existing surveillance is susceptible to under- and over-representation. It is important to determine more accurately the true contribution of undetected or under-detected spotted fever group rickettsial pathogens, and the contribution caused by remote exposures to nonpathogenic or possibly minimally pathogenic agents, such as *Rickettsia amblyommatis, R. montanensis,* or *R. andeanae,* that result in non-specific background seroprevalence.

Passive surveillance for anaplasmosis and ehrlichiosis underestimates the prevalence of these infections since it may rely on multiple factors, including the state's case definition of the disease and voluntary physician/healthcare system reporting. Passive surveillance also fails to capture subclinical and undiagnosed cases, since these do not come to the attention of healthcare providers. Evidence of disease underestimation can be seen by comparing data collected using active surveillance methods with those collected using passive surveillance methods. An active-to-passive surveillance ratio of 11 (whereby passive surveillance data is multiplied by a factor of 11 to estimate the actual number

of cases) was calculated for *Anaplasma phagocytophilum* based on multiple published studies using active surveillance methods (J. S. Bakken et al., 1996; CDC, 2018c; Dumler & Pritt, 2019; IJdo et al., 2000). Similarly, a prospective study of *Ehrlichia chaffeensis* infection revealed fifty-fold higher incidence than the passive surveillance data (Olano et al., 2003). While this study was conducted in the state of Missouri, the location represented what could be considered a typical setting of lone star tick-white tailed deer ecology.

Recommendations

The Working Group identified the following recommendations that the Federal government could initiate to significantly improve the capacity to detect, report, and respond to tick-borne disease threats.

Recommendation 8.1: Fund prospective studies of acute febrile illnesses to assess the burden of tick-borne diseases, including rickettsial, ehrlichial, and anaplasmal pathogens.

A criticism of tick-borne disease diagnostics is that many patients report illness following a tick bite but test negative for any specific pathogen. There are many reasons that could explain why this might occur, including the narrow window of time during which the pathogen may be circulating and therefore detectable in peripheral blood, as is the case for *Borrelia burgdorferi*. Consequently, serology has been the primary tool for laboratory testing for most tick-borne diseases. Detectable antibodies, however, are generally not present early in illness when patients first seek evaluation. For this reason, there is a significant focus on the development of more sensitive direct diagnostic tests.

However, another reason why patients may present with a negative diagnostic test is because their illness may be due to a novel tick-borne pathogen that is not included in the battery of tests that are currently available. In the last 15 years, seven novel tick-borne pathogens have been identified, largely through non-systematic efforts to search for new pathogens (Rosenberg et al., 2018). This observation suggests that more attention should be given to conducting pathogen discovery work in patients with illness following a tick bite. New technologies utilizing metagenomics have led to the detection of novel tick-borne pathogens in patients with undifferentiated acute febrile illness, such as *Borrelia mayonii*.

One approach to increasing our knowledge of tick-borne pathogens is to conduct large-scale studies utilizing blood samples collected from persons who have developed illness following a tick bite, such as the study referenced in the Background section of this chapter. The collaborative study, which involved CDC, the Mayo Clinic, and the Minnesota Department of Health evaluated patient samples only for bacterial pathogens (Kingry et al., 2018). Additional studies should be done to test for novel viral pathogens and to evaluate greater numbers of samples from diverse geographic regions. Information from these studies together with whole-genome sequencing work can be used to develop new and improved direct diagnostic tests.

Recommendation 8.2: Recommend that CDC work with the Council of State and Territorial Epidemiologists (CSTE to streamline the surveillance process and to reduce the burden on clinicians and public health departments by permitting direct laboratory reporting of positive cases.

Under-reporting is a common phenomenon for most high-incidence diseases, and Lyme disease under-reporting is further complicated by a surveillance case definition that requires both laboratory and supportive clinical data for confirmation of all but the earliest manifestations of the illness. In 2018, Lyme disease was the most common vector-borne disease reported and among the top 10 most common of all nationally notifiable diseases (CDC, 2018b). While about 35,000 cases of Lyme disease are reported each year to CDC, recent studies indicate that the actual number of annual cases approximates 300,000 (Hinckley et al., 2014; Nelson et al., 2015). Accurate and up-to-date incidence data for all tick-borne diseases, including Lyme disease, are critical to establish baselines against which to measure prevention efforts and to monitor disease emergence in new geographic areas, as well as to estimate the burden of illness in terms of both economic costs and human suffering.

While direct reporting by laboratories will increase the number of reported cases, it is important to realize that the positive predictive value of laboratory test results for Lyme disease is highly dependent on the prior probability that the patient has Lyme disease (Seltzer & Shapiro, 1996; Tugwell et. al., 1997). Prior probability depends on both the clinical and the epidemiologic history. For example, many positive laboratory test results from areas in which endemic transmission of Lyme disease has never been documented will be false-positive results. Consequently, it will be important to separate cases based solely on positive laboratory test results from traditional case reports. It is also important to note that the geographic distribution of Lyme disease has expanded significantly over the last 20 years (Kugeler, Farley, Forrester, & Mead, 2015) coincidental to the expansion of the key tick vector *I. scapularis* (R. J. Eisen et al., 2016). Moving forward, as the distribution of the vector and subsequent risk for infection expands, the prior probability of infection is likely to change in locations affected by this expansion.

As discussed previously, under-reporting is similarly a challenge for other tick-borne diseases including anaplasmosis, ehrlichiosis, and spotted fever rickettsiosis for various reasons. Based on passive surveillance, more than 5,500 cases of tick-borne spotted fever group (SFG) rickettsioses (caused by *Rickettsiae* in the spotted fever group) were reported in 2018 (CDC, 2018c). These cases do not reflect the true incidence of infections since many cases go unreported. Unfortunately, 99 percent of reported cases are not confirmed (Binder, Nichols Heitman, & Drexler, 2019). At present, serologic diagnosis does not distinguish between patients exposed to the various SFG *Rickettsia* species that human-biting ticks carry in the U.S. Patients exposed to non-pathogenic *Rickettsiae* may develop antibodies that cannot be distinguished from those stimulated by pathogenic species, including the highly virulent *R. rickettsii*, the cause of Rocky Mountain spotted fever, which results in fatality rates exceeding 20 percent in cases where treatment is delayed (Kirkland et al., 1995). Exposure rates are relatively high, with 10–20 percent of healthy persons residing in the region of the U.S. where lone star ticks predominate demonstrating anti-SFG rickettsial antibodies (CDC, 2020g; G.S. Marshall et al., 2003).

Efforts to standardize the surveillance process for all tick-borne diseases should be discussed between CSTE and CDC, including the diseases mentioned above (Lyme disease, anaplasmosis, ehrlichiosis, and spotted fever rickettsiosis) and babesiosis. Additionally, there should be ongoing discussions about the need to include additional tick-borne diseases in the list of nationally notifiable diseases and conditions, should the need arise. A standardized reporting system could be one that under-reports disease cases but can be sustained consistently from year to year and from state to state. Such a system would then allow determination of standard rates of under-reporting and better estimates of disease burden and trends.

Recommendation 8.3: Further evaluation of non-tick bite transmission of Lyme disease, for example maternal-fetal transmission.

The Clinical Aspects of Lyme Disease Subcommittee of the Tick-Borne Disease Working Group considered the role of maternal-fetal transmission of Lyme disease. There is limited evidence linking gestational Lyme disease to adverse pregnancy outcomes (Gardner, 2001; Lakos & Solymosi, 2010; Waddell, Greig, Lindsay, Hinckley, & Ogden, 2018; Walsh, Mayer, & Baxi, 2007). While it appears that the prognosis for the fetus is favorable when gestational Lyme disease is promptly diagnosed and treated with appropriate antibiotics, untreated gestational disease is associated with a higher rate of adverse pregnancy outcomes (Lakos & Solymosi, 2010; Waddell et al., 2018). Although a broad spectrum of adverse fetal outcomes has been noted, a congenital syndrome has not been identified (Gardner, 2001; Walsh et al., 2007).

Additional studies of the incidence of potential maternal-fetal transmission and other non-traditional modes of transmission including blood transfusion, stem cell, other vectors, etc. of *B. burgdorferi* could provide information to help answer frequently asked questions and assumptions about transmission. Similarly, additional studies of potential congenital Lyme disease, and of persistent Lyme disease in undiagnosed and untreated infants resulting from maternal transmission of *B. burgdorferi*, could be helpful, as could patient registries.

The subcommittee also considered findings related to the potential sexual transmission of Lyme disease (Stricker & Middelveen, 2015). The subcommittee concluded that there was limited evidence to support sexual transmission of Lyme disease, given the lack of epidemiological evidence and the seasonality of Lyme disease, among other factors, along with concerns by some subcommittee members regarding the methodology used to support the findings. However, because of the implications of sexual transmission, some members recommended that further studies be conducted to validate or refute this possible mode of transmission, but the potential action is of low priority.

Minority Response: Effect of Geographic Restrictions on Lyme Diagnosis

Access to care, as defined by the National Academy of Medicine, is "the timely use of medical care to obtain the best possible outcome." With regard to Lyme disease, the Training, Education, Access to Care, and Reimbursement Subcommittee was concerned that additional geographic restrictions added to the surveillance case definition in 2017, have lulled clinicians in "low-incidence" states into mistakenly discounting a potential Lyme disease diagnosis. The resultant diagnostic and therapeutic delays that patients in those states have already reported have subsequently limited their ability to obtain their best possible outcome. To reduce this diagnostic hurdle, the subcommittee recommended that "CDC provide input to the Council of State and Territorial Epidemiologists, CSTE, that the Lyme disease surveillance case definition be revised such that it abandons the use of geographic parameters for Lyme disease" and that "CDC, NIH, and other government agency websites, brochures, and educational materials abandon the use of geographic parameters for the diagnosis of Lyme disease and inform clinicians and the public that Lyme disease has been reported in all states" (Training, Education, Access to Care, and Reimbursement Subcommittee, 2020). This Minority Report specifies why the geographic proviso should not have been removed from the Working Group report as a recommendation to Congress.

In moving to a state-based designation, the surveillance case definition has misled clinicians regarding the risk of Lyme disease in their area. Lyme disease exposure is largely driven by geographical terrain and climatic factors. Because these elements vary within a state, state-based incidence definitions obscure the risk for patients exposed in localized "hot spots." As detailed in the subcommittee's report, outside data sources Quest and Fair Health, the latter with a database of 23 billion healthcare insurance claims, show that CDC statistics on low-incidence states are inaccurate (Lee-Lewandrowski, Chen, Branda, Baron, & Kaurman, 2019; McGinty, 2018). Additionally, instituting more stringent requirements for what constitutes a confirmed *erythema migrans* case in low-incidence states results in under-counting of cases and sets up a self-perpetuating cycle for a low-incidence designation as doctors there often are not diagnosing and treating. They are frequently concerned about the ramifications from medical boards who have sanctioned physicians in some circumstances.

Additionally, when clinicians underestimate their patients' risk of Lyme disease, they may mistakenly discount true cases of the infection and lengthen the time to diagnosis and treatment. Patients misdiagnosed because of geographically-based misconceptions often have to travel to distant states for a willing and knowledgeable clinician and are likely to experience treatment delay, which increases their risk of developing persistent Lyme disease. As noted in the subcommittee's report, a survey of patients with persistent Lyme disease documented that 70% reported substantial diagnostic delays (Johnson, Shapiro, & Mankoff, 2018). Diagnostic delays can be costly; the total averaged cost of treating late Lyme disease is approximately $24,000 per year, which is 12 times higher than the cost of treating early Lyme disease (Johnson, 2019; Zhang et al., 2006). The report also details the substantial

consequences that persistent Lyme disease has on patients' lives: 72% of patients with chronic Lyme disease reported their health status as fair or poor and 75% experienced severe or very severe symptoms; many are unable to regularly attend school or hold down a job (Johnson, Wilcox, Mankoff, & Stricker, 2014).

Given the negative impacts on access to care for Lyme disease that geographic parameters in the surveillance case definition impose on clinicians and patients, the subcommittee's initial recommendation on CDC recommending review of the geographic diagnostic restrictions should have remained intact.

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Chapter 9
Federal Inventory

Recommendations at a Glance: Federal Inventory

Recommendation 9.1: VA: Recommend that the VA continue with *Recommendation 8.4* from 2018 Working Group report, "Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members" and additionally

- Establish and update efforts on tracking and investigating the prevalence of Lyme and other tick-borne diseases; and
- Make educational modules available to practitioners.

Recommendation 9.2: DoD: Recommend that the DoD enhance inter-agency communication and collaboration to study Lyme disease and other tick-borne diseases.

Recommendation 9.3: CDC: Recommend that **if** the CDC posts any Lyme treatment guidelines, that they include guidelines on persistent Lyme Disease.

Recommendation 9.4: NIH: Recommend that the NIH create one or more study sections composed of members whose expertise is human clinical diseases and their pathogenesis and immunity not just basic science to evaluate applications focused on practical impact on human health related to tick-borne diseases.

Recommendation 9.5: NIH: Recommend that NIH receive additional funding which must be dedicated to study Lyme disease including persistent Lyme disease and other tick-borne diseases and conditions; and they encourage researchers to apply for these studies.

Recommendation 9.6: CMS: Recommend that CMS provides all information and data on Lyme disease and other tick-borne diseases and all applicable agency activities pertaining to these conditions which may include but should not be limited to:

- Reimbursement costs for the diagnosis and treatment of beneficiaries with Lyme disease and other tick-borne diseases;
- Demonstration and pilot projects with Lyme disease and other tick-borne diseases as their focus; and
- Quality measure development and implementation related to Lyme disease and other tick-borne diseases.

Background

The Tick-Borne Disease Working Group (hereafter, the "Working Group") was established through the *21st Century Cures Act*, which provides that the Working Group should review all efforts within the Department of Health and Human Services to ensure interagency coordination, minimize overlap, and examine research priorities in the area of tick-borne diseases. To that end, the Working Group developed inventories (Appendix F) and submitted them to Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), National Institutes of Health (NIH), U.S. Department of Defense (DoD), U.S. Department of Veterans Affairs (VA), U.S. Department of Agriculture (USDA), and U.S. Food and Drug Administration (FDA). To process the inventories received by each agency, The Working Group's Federal Inventory Subcommittee reviewed and summarized the following results. The complete inventory survey results can be obtained by any individual who submits a request through the Tick-Borne Disease Working Group emailbox: tickbornedisease@hhs.gov.

Of the Working Group's focus areas, CDC, NIH, and DoD have addressed all but access to care. CDC and NIH each have a strategic plan for addressing tick-borne diseases and DoD has a strategic plan for its Congressionally Directed Medical Research Program (CDMRP), which awards grants. CDC has engaged in human surveillance, while CDC, NIH, and DoD have participated in animal surveillance. USDA and CDC have addressed disease vectors, surveillance, and prevention, and VA has addressed access to care services. FDA is a regulatory agency and does not have dedicated funding for tick-borne diseases. Most of its activities related to the regulation of drug products for tick-borne disease are funded through user fees. CMS provided 2016 information on Medicare fee-for-service utilization and payments associated with Lyme disease. In 2016, there were 226,763 claims for Lyme disease based on any ICD-10 diagnostic codes, and the total reimbursement payment was $138,743,558.

Of note, the Federal Inventory questionnaire developed for all the agencies by the Tick-Borne Disease Working Group was found not to be tailored to CMS activities. Therefore, CMS was not able to provide much information about its tick-borne disease activities. The Working Group should consider redevelopment of the CMS inventory questions for its 2022 Report to Congress.

When reviewing the Federal Inventory results, the Working Group observed enhanced funding and research activities at CDC and NIH after the submission of the Tick-Borne Disease Working Group 2018 Report. CDC supports a wide range of intramural and extramural projects and activities related to tick-borne disease, including national surveillance for both ticks and human illness. In response to the Tick-Borne Disease Working Group 2018 Report to Congress (https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf), CDC led the development of a multi-agency National Public Health Framework for the Prevention and Control of Vector-Borne Diseases in Humans.

Similarly, NIH continues to support an extensive research portfolio that includes basic and some clinical studies aimed to 1) improve rapid and accurate diagnostic test, 2) understand the immunological mechanism of immune protection for Lyme diseases and other tick-borne diseases, and 3) develop antibiotic combination and/or therapeutic options for treating acute and persistent tick-borne illness.

In response to the 2018 Report, NIH developed and published in October 2019 the NIH Strategic Plan for Tick-Borne Disease Research (https://www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf).

Based on Federal Inventory results, the Working Group identified the following needs and gaps in research.

- Update efforts on tracking and investigating the prevalence of Lyme disease and other tick-borne diseases, for example, within the Defense Health Agency (DHA), and make the education modules available to practitioners.
- Increase NIH funding to support research on Lyme disease (particularly persistent Lyme disease) and other tick-borne diseases.

Recommendations

The Working Group has identified six recommendations to Congress that Federal agencies can implement to further the study of Lyme disease and other tick-borne diseases.

Recommendation 9.1: VA: Recommend that the VA continue with Recommendation 8.4 from 2018 Working Group report, "Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members" and additionally

- Establish and update efforts on tracking and investigating the prevalence of Lyme and other tick-borne diseases; and
- Make educational modules available to practitioners.

Servicemembers, their families, and Veterans are especially vulnerable to tick-borne diseases and conditions through field exercises and extensive travel to areas of high risk. To ensure their safety and protect the investment of the American public in the Armed Forces, the Working Group requests that VA develop a concrete plan to address the effect of tick-borne diseases on Veterans and to implement an educational program for healthcare providers.

Recommendation 9.2: DoD: Recommend that the DoD enhance inter-agency communication and collaboration to study Lyme disease and other tick-borne diseases.

DoD supports activities relevant to tick-borne diseases such as active surveillance of infectious diseases in military personnel around the world and of the presence and geographic distribution of human pathogens, and the control of ticks to which Servicemembers may be exposed. The Working Group urges continuation of these activities with a strong focus on communication and collaboration between the broader relevant DoD agencies regarding tick-borne diseases.

Recommendation 9.3: CDC: Recommend that **if** the CDC posts any Lyme treatment guidelines, that they include guidelines on persistent Lyme Disease.

CDC currently lists treatment guidelines for early Lyme disease. **If** those guidelines continue to be posted on their website, there needs to be some statement that acknowledges the existence of persistent Lyme disease, and that there is currently not sufficient information regarding causation of these symptoms to provide any guidelines regarding specific treatment recommendations, and that management of the continuing symptoms is up to the individual healthcare provider.

Recommendation 9.4: NIH: Recommend that the NIH create one or more study sections composed of members whose expertise is human clinical diseases and their pathogenesis and immunity not just basic science to evaluate applications focused on practical impact on human health related to tick-borne diseases.

In the field of research on tick-borne diseases, NIH study sections primarily consist of members focused on the frontier of basic science itself with few members devoted to the study of diseases and their pathogenesis. Furthermore, translational research study sections, such as for vaccines, tend to promote research on advanced rather than early-development interventions. Thus, there seems to be a gap in research toward translational advances.

Some tick-borne diseases are acute and life-threatening. There is a short window of time to consider the diagnosis and start appropriate treatment. For these diseases the usual empiric regimen of antibiotics that is used for sepsis is not effective. Appropriate treatment given early in the course of illness prevents death and shortens the illness. Therefore, more attention needs to be placed on diagnosis and treatment of the acute illnesses, including acute Lyme disease, spotted fever group rickettsioses, human monocytic ehrlichiosis, human granulocytotropic anaplasmosis, and babesiosis. Diagnostic as well as therapeutic issues remain an important problem for the entire spectrum of Lyme disease, from its earliest manifestations to its persistent symptoms, and addressing these issues is urgently needed so that healthcare providers have the needed tools and treatments to better diagnose the disease and treat patients with the disease.

Prevention of all tick-borne diseases is most effectively accomplished by the best public health weapon available, namely development of vaccines. Thus, research should also focus on the development of anti-tick borne disease vaccines that include protection against multiple high-consequence pathogens (*Borrelia burgdorferi, Rickettsia rickettsii, Ehrlichia chaffeensis, Anaplasma phagocytophilum, Babesia microti*, and Powassan virus), and protection against the tick itself to prevent pathogen transmission.

Recommendation 9.5: NIH: Recommend that NIH receive additional funding which must be dedicated to study Lyme disease including persistent Lyme disease and other tick-borne diseases and conditions; and they encourage researchers to apply for these studies.

The NIH tick-borne diseases portfolio of funded research contains predominantly basic science projects, for example those related to pathogen-host cell interactions. Yet we need to understand the basis of long-lasting symptoms in patients with a diagnosis of Lyme disease. It is unclear that the patients continue to have *B. burgdorferi* in their body or that, if a small quantity of organisms or antigen is present, it is playing a role in patients' symptoms. An understanding of the mechanisms of the chronic illness is required in order to develop therapeutic countermeasures in addition to antibiotics.

Although there are many acute tick-borne diseases in the United States, some of them life-threatening and—in the case of the viral diseases—untreatable, the loudest voices have been focused on the chronic symptoms attributed to Lyme disease. Persons with these conditions suffer, often without effective response to treatment. The principal obstacle to curing these symptoms is lack of knowledge of the pathogenic mechanisms that are causing the debilitating illness. Efforts need to be directed to determining the causes, whether owing to the hypothesis of pathology stimulated by a chronic *Borrelia* infection or investigation and elucidation of other pathogenic mechanisms unrelated to active infection with *B. burgdorferi*.

Recommendation 9.6: CMS: Recommend that CMS provides all information and data on Lyme disease and other tick-borne diseases and all applicable agency activities pertaining to these conditions which may include but should not be limited to:

- Reimbursement costs for the diagnosis and treatment of beneficiaries with Lyme disease and other tick-borne diseases;
- Demonstration and pilot projects with Lyme disease and other tick-borne diseases as their focus; and
- Quality measure development and implementation related to Lyme disease and other tick-borne diseases.

It is important that reimbursement costs for Lyme disease and other tick-borne diseases be tallied and released publicly in order to use that data to help with issues such as access to care for patients across the United States.

Chapter 10
Public Input

There was a general consensus among public commenters that enhanced education for the public and healthcare providers, improved diagnostic tools, and safer, more effective treatment options for persistent symptoms of Lyme disease are urgently needed. The public would like to see increased research funding, further scientific exploration, and unbiased and fresh reviews of the latest information across all related sectors. Public comments are summarized in this chapter and organized as they relate to the Tick-Borne Disease Working Group's priority areas and overall processes.

Tick Biology, Ecology, and Control

Public commenters called for prioritization of tick research, with a focus on proactively reducing tick populations and blocking the ability of ticks to transmit pathogens. Other commenters noted that tick control should be a priority, and specific requests were made by the public to leverage advances in science and technology for this purpose (for example, gene editing, CRISPR, nootkatone).

While some public commenters noted the need to address the loss of deer habitat, stating that it is bringing ticks into closer contact with humans, others suggested that deer are also victims to ticks and not the root of the problem.

Several public commenters pointed out that additional funding is needed for the immediate implementation and subsequent monitoring of education and prevention programs.

Clinical Manifestations, Diagnosis, and Diagnostics

Public commenters highlighted the wide spectrum of symptoms of tick-borne diseases, including Alpha-gal Syndrome, and called for attention to tick-borne disease patients experiencing multiple chemical sensitivity. Public commenters cited the misdiagnosis of chronic Lyme disease (for example, as fibromyalgia, multiple sclerosis, and lupus), urging increased awareness and research of the breadth of complex neurologic, cardiac, and musculoskeletal symptoms that may be involved.

Persistent Lyme disease symptoms cited in the public comments included: musculoskeletal pain, cramps, twitches, bladder pain, severe/chronic fatigue, swollen joints, arthritis, heart arrhythmias, Bell's palsy, numbness, foot drop, inflammation, food allergies, digestive issues, skin issues, light/noise/tactile sensitivities, and neurological issues such as headache, depression, anxiety attacks, disturbances in emotional regulation, insomnia, slurred speech, and challenges in cognition, concentration and memory.

Multiple public commenters pointed out the need for better diagnostic tools and standards to ensure early and accurate tick-borne disease diagnosis to address often dangerous acute manifestations (for example, anaphylactic shock with Alpha-gal Syndrome and sepsis with Rocky Mountain spotted fever) before disabling long-term sequelae can occur. The role of DNA and metagenomics sequencing were cited by the public as possible detection methods and improvements to tick-borne disease diagnostics.

In the case of Lyme disease, public commenters noted that current serological testing is limited due to the transient presence of *Borrelia burgdorferi* in the blood, and CDC guidelines are inaccurate, thus hindering clear diagnosis and course of treatment.

Causes, Pathogenesis, and Pathophysiology

The public fundamentally requests clinical research trials to understand the causes of Lyme disease and how and why infection persists. Public commenters requested clarification of the risk of contracting Lyme disease via studies that clearly link minimum amount of tick attachment time to transmission of the disease in humans, as well as research into the pathology of the human response following a tick bite, including clearer understanding of the influence of the tick microbiome.

Additional commenters suggested that research address issues associated with the human immune system, both the role of the immune system in the pathogenesis and pathophysiology of tick-borne disease and the impacts of tick-borne disease on the immune system (immunodeficiency), including tick-borne sepsis and the implications of reactivation of viruses not associated with tick bite.

Public commenters also suggested assessing the risk of disease transmission through blood transfusion, organ and tissue transplantation, use of stem cells, and other mechanisms including maternal to fetal transmission and the possibility of sexual transmission. Some commenters encouraged more research into the causes of longer-term symptoms of Lyme disease in patients who continue to experience symptoms after recommended antibiotic treatment, and whether those symptoms are attributed to persistent infection. References were provided in support of the existence of persistent Lyme disease.

Treatment

As members of the public support early and aggressive treatment for Lyme disease, others commented that a short antibiotic course does not always cure the disease, as patients may require long-term triple antibiotic treatment. It was noted that patients improve while receiving antibiotic treatment for Lyme disease, but that for some their symptoms return and their condition worsens when they stop treatment.

Several public commenters indicated that research has not sufficiently addressed persistent symptoms of Lyme disease, and other tick-borne diseases such as Rocky Mountain spotted fever. Additional commenters called for increased research funding to address treatment-resistant infections and persistent symptoms of tick-borne diseases. Members of the public, however, also warned of the potential harm of prolonged use of antibiotics and other drugs to patient health. In many instances, the public made reference to amendment of the CDC guidelines for persistent Lyme disease, noting that the recommended doxycycline regimen does not cure post-treatment Lyme disease.

Public commenters generally agreed that safe and effective alternative treatments to what is currently available (for example, novel antimicrobial chemotherapies) are needed to help patients with tick-borne diseases, particularly those with multiple tick-borne illnesses and those suffering from chronic illness.

The public noted that treatment failure rates remain unacceptably high for Lyme disease, as (prior) clinical trials have been too small to allow for the collection of real-world evidence pertaining to

treatment response. It was emphasized that treatment trials should be focused on delivering outcomes to support specific patient subsets that may experience different symptoms, and that other clinical development tools should be leveraged, such as patient registries, to aid in trial design, recruitment, and the collection of real-world evidence.

Education and Access to Care

Public commenters indicated that tick-borne diseases, in particular Lyme disease, are still minimized and patients are commonly denied care by clinicians. The public highlighted the need to improve clinician training and education on the broad range of tick-borne disease symptoms and appropriate methods of diagnosis, in all states across the country. Multiple commenters raised concerns over low awareness among clinicians of all tick-borne diseases, which often results in delayed diagnosis or misdiagnosis, delayed treatment, and patient suffering, particularly in those with persistent Lyme disease, Rocky Mountain spotted fever, and Alpha-gal Syndrome.

Tied to concerns about increased awareness, training, and education of clinicians, the public called for the empowerment of practitioners to feel comfortable making a tick-borne disease diagnosis on record without fear of compromising their careers or reputations.

Additional commenters pointed out the need for more, accurate, evidence-based educational materials on tick-borne diseases for the general public in all states.

Concern was expressed that CDC guidelines for Lyme disease and tick-borne disease management create challenges or obstacles for patient care and reimbursement, and that it would be beneficial to include both the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS) guidelines on various government websites.

Public commenters indicated that access to care is poor and reimbursement is inadequate or non-existent, hindering effective treatment. Military Servicemembers and Veterans further report difficulty accessing affordable care. It was suggested by public comment that accepting new ICD-11 codes that include updated information regarding Lyme disease would be a great start to improving patient access to care. Concerns were raised by the public about the financial impacts that tick-borne diseases can have on individuals and families, as well as emotional impacts including depression, substance abuse, and increased suicidality, and it was suggested that Lyme disease should qualify patients for disability benefits.

Multiple commenters expressed that denying the existence of persistent Lyme disease, and the lack of insurance coverage for treatments, is an insult and injustice to the many patients who have lived with the effects of the disease for years, with comments coming from patients a few years after a tick bite to more than 25 years post-tick bite.

The public has requested support for Lyme disease and other tick-borne diseases analogous to what is available for other chronic diseases such as cancer, and noted that ultimate treatment decisions should fall solely on the patient. Public commenters also stressed that insurance needs to cover tick-borne disease treatment beyond short-term oral antibiotics, specifically noting that treatments for persistent Lyme disease are lacking and/or not covered.

Epidemiology and Surveillance

Public commenters noted the importance of enhanced national surveillance.

Commenters also suggested that, to aid in diagnosis, CDC should inform physicians that Lyme disease is endemic in every state.

Process

Several public commenters requested increased transparency of the selection process for Working Group members and full disclosure of Working Group member conflicts of interest. They also stressed the need for increased patient representation and involvement of individuals who do not deny the existence of persistent Lyme disease.

The public expressed concern with the voting processes used by the Working Group, including the use of proxy votes in the absence of Working Group members and the practice of abstaining from voting on controversial issues.

Additional public commenters suggested improving responsiveness and timeliness from Health and Human Services when responding to emails and making announcements.

Written public comments submitted for the Tick-Borne Disease Working Group public meetings can be viewed by clicking on the individual meetings listed at the following link: https://www.hhs.gov/ash/advisory-committees/tickbornedisease/meetings/index.html.

Chapter 11
Looking Forward

The Tick-Borne Disease Working Group 2020 Report to Congress identifies critical unmet needs in the following areas:

- Tick Biology, Ecology, and Control
- Clinical Manifestations, Diagnosis, and Diagnostics
- Causes, Pathogenesis, and Pathophysiology
- Treatment
- Clinician and Public Education, Patient Access to Care
- Epidemiology and Surveillance

The report includes recommended actions that Congress and the Secretary of Health and Human Services can take to address these needs.

Yet as we look forward to the future, more can always be done. Clinicians need better tools to diagnose and more resources to treat individuals struggling with tick-borne diseases and conditions.

Expand Collaboration to Drive Innovation and Improve Patient Care

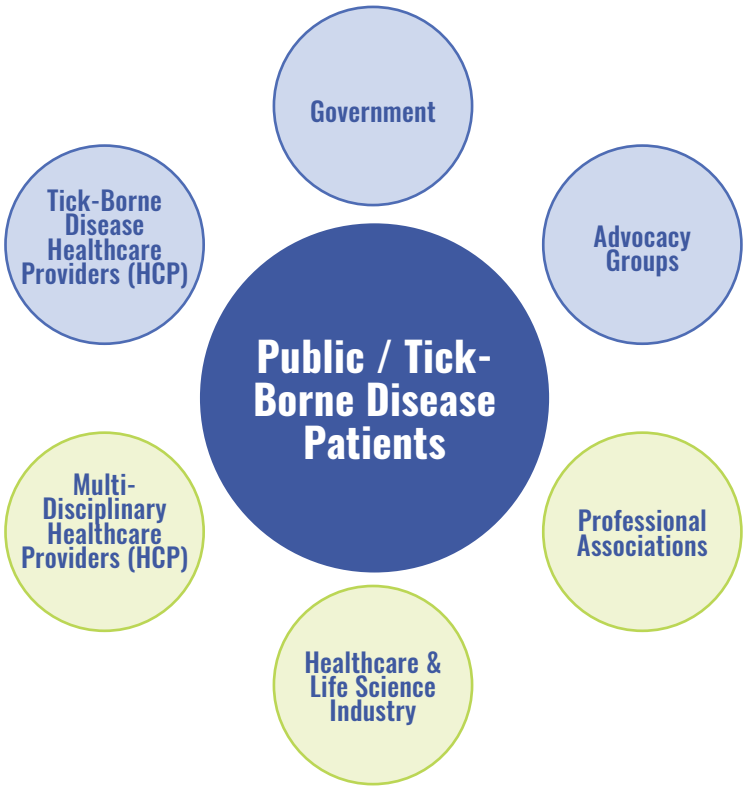
In recent decades, there is a groundswell of consistent effort among members of the public, the scientific community, healthcare providers, advocates, and constituents who dedicate their voices and professions to crusade for positive change in Lyme disease and other tick-borne diseases and conditions. Their invaluable work has gotten us where we are today. However, to measurably push the needle forward in tick-borne diseases, we must challenge the status quo. We must ask ourselves:

Who else should we engage in this process to advance our efforts?

What other disciplines can we learn from to forge ahead with the most impact?

The Working Group underscores several core values (p. 107), two of which are collaboration and innovation. Outreach to a broader group of stakeholders who have not yet been *fully* brought into the Lyme disease and tick-borne disease fold (Figure 9), embraces these values and may provide novel insights and new sources of information to achieve even more healthy progress in tick-borne diseases.

Figure 9: Broaden the Sphere of Stakeholder Influence



Pathway to Novel Treatments and Improved Patient Quality of Life

Cross-stakeholder collaboration is an avenue to innovation—such as through advancing treatments for Lyme disease and tick-borne disease patients—and, ultimately, the quality of patient lives.

Align on Unmet Need

For example, the life science industry—encompassing the fields of biotechnology, pharmaceuticals, biomedical technologies, healthcare technologies, botanical science and crop technologies, veterinary fields, and environmental sciences (Torres, 2019)—plays a critical role in research, development, and a broad range of commercialization efforts that include assisting with bringing products to market and securing their availability to patients. Therefore, through improved life science industry outreach, there is an opportunity to provide awareness and education as well as foster a greater understanding and interest in tick-borne diseases. This is critical as pharmaceutical companies, specifically, support "the discovery, development, and manufacture of drugs and medications" (Dailey, 2020) and have a direct impact on public health and patients with tick-borne diseases.

Through a greater alliance, researchers, scientists, providers, patients, and members of the public can advocate for unmet patient need, necessitating a demand for novel, innovative therapies, particularly for patient segments that do not respond to current treatments and/or that experience relapse. Better informed industry stakeholders are better equipped to support and prioritize tick-borne diseases and unmet patient need, as well as invest in new product development. The result of a stronger, greater alliance with industry is that tick-borne disease patients, providers, and payers can ultimately benefit from future innovations—those that otherwise may not have been on the horizon.

Development of new treatments. Industry stakeholders are a necessity in the advancement of tick-borne disease treatments through a) scientific and clinical research studies and b) manufacturing, distribution, and commercialization of new products.

Multi-disciplinary Approach

Lyme disease patients often suffer from symptoms that overlap with other diseases and conditions, including migraines, cardiac issues, cognitive diseases, and autoimmune illnesses, many of which have well-established treatment options. Broader outreach to stakeholders (including providers, scientists, researchers, and industry) who address these therapeutic spaces could greatly expand the potential for improved symptom management for Lyme disease patients. For example, cross-disciplinary collaboration could enable patients with Lyme disease and Alpha-gal Syndrome to be considered for inclusion in pre-market or scientific studies for supportive care treatments (for example, symptom management) and/or to benefit from shared patient management strategies.

Additionally, collaborating with stakeholders in other medical disciplines could create opportunities to investigate new tick-borne disease drug uses, therapy applications, or novel "cocktail" protocols, a common practice in oncology and other therapeutic applications (Breastcancer.org, 2018; Feng, Leone, Schweig, & Zhang, 2020; Hu, Sun, Wang, & Gu, 2016; Jordan et al., 2017). As we look to the future of care in tick-borne diseases, we must ask ourselves the following questions:

Why aren't we broadening our learning to other multi-disciplines?

What can be the role of supportive care in aiding patients?

What else can be shared from other therapeutic disciplines?

Communication

It cannot be ignored that lessons learned from the efforts, collaboration, and studies related to COVID-19 may one day be applicable to Lyme disease and other tick-borne diseases. These experiences are still too new for their impact to be fully understood. Yet, the unprecedented national response has demonstrated what is possible when all stakeholders—including Federal, state, and local government, the scientific and medical communities, industry, and the general public—collaborate with a sense of purpose, urgency, and dedication to a serious public health issue. However, these successes and potential lessons cannot be applied to minimize the threat of Lyme disease and other tick-borne diseases if they are not communicated and shared.

The future of Lyme disease and tick-borne diseases requires an all-hands-on-deck approach, requiring the engagement and collaboration of a wide range of stakeholders that share one common goal: to do what's best for patients. Current tick-borne disease stakeholders are encouraged to enhance and expand collaboration and outreach not only with each other, but also with stakeholders who can 1) advance research and innovation in the areas of unmet need, and 2) provide interdisciplinary insights and resources that have the potential to alleviate or positively impact symptoms and improve the quality of patient care.

Core Values to Achieve One Shared Vision

Shared Vision: A nation free of tick-borne diseases where new infections are prevented and patients have access to affordable care that restores health.

RESPECT:
Everyone is valued

We respect all people, treating them and their diverse experiences and perspectives with dignity, courtesy, and openness, and ask only that those we encounter in this mission return the same favor to us. Differing viewpoints are encouraged, always, with the underlying assumption that inclusivity and diversity of minority views will only strengthen and improve the quality of our collective efforts in the long term.

INNOVATION:
Shifting the paradigm, finding a better way

We strive to have an open mind and think out of the box. We keep what works and change what doesn't. We will transform outdated paradigms when necessary, in order to improve the health and quality of life of every American.

HONESTY & INTEGRITY:
Find the truth, tell the truth

We are honest, civil, and ethical in our conduct, speech, and interactions with our colleagues and collaborators. We expect our people to be humble, but not reticent, and to question the status quo whenever the data and the evidence support such questions, to not manipulate facts and data to a particular end or agenda, and to acknowledge and speak the truth where we find it.

EXCELLENCE:
Quality, real-world evidence underlies decision-making

We seek out rigorous, evidence-based, data-driven, and human-centered insights and innovations—including physician and patient experiences—that we believe are essential for scientific and medical breakthroughs. We foster an environment of excellence that strives to achieve the highest ethical and professional standards, and which values the development of everyone's skills, knowledge, and experience.

COMPASSION:
Finding solutions to relieve suffering

We listen carefully with compassion and an open heart in order to find solutions which relieve the suffering of others. We promise to work tirelessly to serve the greater good until that goal is achieved.

COLLABORATION:
Work with citizens and patients as partners

The best results and outcomes won't be created behind closed doors, but will be co-created in the open with input of the American public working together with these core values as our guide. We actively listen to the patient experiences shared with us, respect the lived experiences of patients and their advocates, and learn from their experiences in our pursuit of objective truth. Across diverse audiences, we communicate effectively and collaborate extensively to identify shared goals and leverage resources for maximum public health impact.

ACCOUNTABILITY:
The buck stops here

We, as diligent stewards of the public trust and the funds provided by our fellow citizens, pledge to be transparent in all of our proceedings and to honor our commitments to ourselves and others, while taking full responsibility for our actions in service to American people.

Minority Response to Industry Representation in Looking Forward

This minority, dissenting opinion addresses the language focusing on outreach to broader groups of stakeholders (in particular, industry stakeholders), in Chapter 11, *Looking Forward*, of the 2020 Tick-Borne Disease Working Group 2020 Report to Congress.

According to the Working Group's section of the Office of the Assistant Secretary for Health's website, "The *21st Century Cures Act*, enacted in December 2016, authorizes the HHS Secretary to establish a Tick-Borne Disease Working Group to serve as a Federal Advisory Committee. The Working Group is to comprise Federal and public members with diverse disciplines and views pertaining to tick-borne diseases. The Act charges the Working Group to provide a report to Congress and the HHS Secretary on its findings and any recommendations every two years. Working Group responsibilities include a review of ongoing research and resulting advances; Federal epidemiological and research efforts; and identification of research gaps." (Tick-Borne Disease Working Group, 2017)

Section 2062(c)(3) of the Act itself clearly delineates the two types and the number of Working Group members: (A) seven Federal members and (B) seven non-Federal public members (*21st Century Cures Act*, 2016). The seven Federal members are clearly described under Sec. 2062(c)(3)(A), which specifically lists four Federal agencies and offices that must have at least one representative on the Working Group and which also allows the HHS Secretary to include representatives from other appropriate Federal agencies and offices. Non-Federal public members are clearly described under Section 2062(c)(3)(B), where four specific categories of non-Federal members are delineated. Unlike the selection of Federal members, the language of the Act does not give the Secretary any discretion to appoint any other categories of non-Federal public members to the Working Group. Under Section 2062(c)(3)(B), the category of healthcare industry representatives is not statutorily included as a valid category for membership on the Working Group.

The legislation does instruct the Working Group to solicit input from "states, localities, and nongovernmental entities, including organizations representing patients, healthcare providers, researchers, and industry regarding scientific advances, research questions, surveillance activities, and emerging strains in species of pathogenic organisms" (Sec. 2062(c)(2)(C)). Thus, the statutory language of the Act does not preclude a healthcare industry representative from being selected to serve as a member of a Working Group subcommittee or from being asked to present as a speaker to such a subcommittee.

The public Working Group discussion of Chapter 11 centered on that very issue; that is, if this chapter (and by extension, the entire report) specifically mentions, supports, and recommends increased and focused outreach to medical industry stakeholders, then prescriptive language must also be included

in the report to correct any misconceptions that Congress and the public might have regarding the Working Group's opinion on the medical industry's role in and its influence on the Working Group, its overall report to Congress, and its recommendations. In other words, the Working Group must clarify the confusing language of this chapter (and in doing so, rectify the misleading nature of this chapter within the context of the rules for Working Group membership in the Act itself) in order to remind us of the very clear and prescriptive statutory language that Congress employed in establishing the parameters for this Working Group's membership. Despite the somewhat nebulous language that the majority of the Working Group publicly approved for this chapter, the Congressional language remains crystal clear—the medical industry and its representatives are *not included* within the four statutorily mandated Working Group non-Federal public member categories, and are, therefore, *excluded* from having a seat on the Working Group.

Prior to the public discussion of Chapter 11, *Looking Forward*, concerns had already arisen on the issue of the medical industry's role on the Working Group and on its influence, as there is one current Working Group member who had continued to self-identify as a *medical/healthcare industry representative*. However, HHS has never publicly stated which non-Federal public members represent which of the statutorily mandated categories defined in the legislation. That fact was pointed out at a public meeting by another Working Group member. The individual self-identifying as a medical/healthcare industry representative was then forced by HHS to identify in the more accurate, applicable, and statutorily defined member category of a *patient (recovered)* in the relevant opening chapter of the report.

Unfortunately, HHS has never entirely rectified this issue, and the member currently remains listed as previously self-identified (i.e., as a *medical/healthcare industry representative*) and is not listed in the statutorily prescribed and more appropriate member category of a *patient (recovered)*, both on the HHS website as well as in portions of this report (as of the drafting of this minority dissenting opinion on November 23, 2020). The Working Group members writing this dissenting minority opinion believe that this situation must be corrected immediately. The individual member in question must be identified in the applicable member category of a *patient*, as mandated in Section 2062(c)(3)(B) of the Act, and all previous identifications of the member as being on the Working Group in the statutorily excluded category of a medical/healthcare industry representative must be removed. (Please note that this discussion of the Congressionally mandated Working Group member categories is in no way intended to malign the reputation of the Working Group individual member in question, nor is it intended as a reflection on the character of that individual; rather it is intended to ensure the present integrity of the Working Group and of the law that established it, and to prevent future instances where that law might be undermined by similarly incorrect and/or questionable applications).

Serious public concerns have arisen over the legislation being subverted in seemingly innocent and presumably unintended ways such as this. The industry-favorable language included in this chapter, coupled with the issue discussed previously of a Working Group member self-identifying as an industry

representative, serve to drive very real public fears over possible conflicts of interest if industry were provided a seat at this table. It would be difficult to filter out those conflicts when individuals are given a vote that could financially impact them.

This *Looking Forward* chapter of the 2020 Tick-Borne Disease Working Group 2020 Report to Congress constitutes three-and-a-half pages, of which two-and-a-half pages are devoted to promoting an agenda that argues for giving the medical/healthcare industry and its paid representatives a seat at that table. The Tick-Borne Diseases Working Group, its mission, and its members are defined by the language of Congress contained within the *21st Century Cures Act*, and its core responsibilities must remain as they are written, including: review of ongoing research and resulting advances; Federal epidemiological and research efforts; and identification of research gaps. Further, the Congressional language clearly delineates the rules and regulations surrounding the Working Groups recommendations, its report, its meetings, and its members. On that last point, membership, the statutory language of the Act itself leaves no room for doubt as to who should be involved and how.

The *21st Century Cures Act* provides a focus on medical and health issues as being patient-centered, giving a real voice to patients, their families, and loved ones, and emphasizing their very real concerns. Putting industry players on the Tick-Borne Disease Working Group is not only bad policy, but it is in direct conflict with the intent and the actual text of the language written and approved by our Congressional representatives. Any move that attempts to circumvent that language and intent, no matter how subtle it might be, would only serve to drastically dilute the voice of patients, to greatly increase the potential for conflicts of interest (especially those of a financial nature), and to enfranchise industry with a vote that must be deserved for those whom Congress designated. As President Dwight D. Eisenhower, in his farewell address to the nation on January 17, 1961, warned, "…we must guard against the acquisition of unwarranted influence, whether sought or unsought by the military–industrial complex" ("Military–industrial complex," 2020), so too must we guard against a similar "acquisition of unwarranted influence" by today's very real and powerful "medical-industrial complex" ("Medical–industrial complex," 2020).

In this dissenting minority opinion on Chapter 11, *Looking Forward*, with its supporting language revealing an apparent industry bias, we are not attempting to irresponsibly demonize the entire medical/healthcare industry. Instead, we are simply and honestly sounding an eerily similar alarm that we must guard against any potential conflicts of interest, rise in unwarranted influence, and naked power grabs by certain elements of the medical/healthcare industry, along with its paid representatives, especially those that seek to silence the voice of patients and to distort and obscure the truth for financial gain and greater influence, regardless of what the devastating cost might be for patients, for their families, and for our nation as a whole.

Regrettably, the voice of the patient has already been diluted for this 2020 term when, at the very outset of this Working Group term, seats previously and appropriately designated for patients were intentionally filled by new public voting members who clearly do not represent patient interests and concerns. A further assault on the very integrity of the Working Group occurred in March 2020 at the

public meeting in Philadelphia, where, for the first time since the Working Group's initial establishment in December 2017, proxy votes were allowed—this then *permitted certain voting members to not be present* at a number of significant discussions (but to still have a say in the outcome of these discussions by way of their proxy votes). It must be stated here that these discussions, the very heart of the Working Group public meetings, were where members (who, it must be assumed, deemed these discussions *important enough to be present*) were attempting to reach consensus on critical and potentially life-altering issues for patients and their families suffering under the burden of Lyme disease and other tick-borne diseases. We believe that this unprecedented and wrong-headed "decision" to allow absentee members to cavalierly give away their votes to someone else, and made by the Working Group Co-Chairs without any opportunity for discussion and/or vote by the Working Group membership on this matter, at the very least, constitutes a serious and problematic breach of the public trust, and, at the very worst, merits an investigation, by an independent investigative body designated by Congress for such matters, into possible violations of FACA and other Federal regulations.

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Patricia V. Smith, BA

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Conclusion

The 2020 Tick-Borne Disease Working Group Report is the second report to the Secretary of Health and Human Services (HHS) and Congress, following the first report in 2018, as requested by the *21st Century Cures Act*. It was developed by cross-functional stakeholders including patients, government officials, physicians, scientists, and public health officials (Appendix A).

The 2020 Report provides recommendations for changes and improvements pertaining to Lyme disease and other tick-borne diseases and conditions, specifically research and activities that the Working Group has identified as necessary to advance public health.

This report identifies the key issues in the field, describes current state of research and medical care, synthesizes Federal activities related to tick-borne diseases and conditions, and highlights comments from the public. It underscores the need to further improve medical education, fund the development of better diagnostic tools and treatment options, support surveillance and prevention efforts, and address the needs of patients affected by Lyme disease and other tick-borne diseases and conditions. Focus areas of this report include:

- Tick Biology, Ecology, and Control
- Clinical Manifestations, Diagnosis, and Diagnostics
- Causes, Pathogenesis, and Pathophysiology
- Treatment
- Clinical and Public Education, and Patient Access to Care
- Federal Inventory
- Public Input

Ths report serves as both a communication tool and a 'Call-to-Action' for the HHS Secretary and Congress. It integrates and coordinates an extensive review of data, expert opinions, and specific steps most needed to deliver positive impact on the devasting and often misunderstood areas of Lyme disease and other tick-borne diseases and conditions. These actions require urgently needed funding to address the growing public health concern and support the care of patients with tick-borne diseases and conditions.

It is important to acknowledge that the 2020 Report development process entails consideration of different perspectives. The Working Group encouraged open dialogue among its members

representing diverse professional roles and perspectives and heard opposing viewpoints. The field of Lyme disease and other tick-borne diseases and conditions is populated with different views, and this report is no different. For areas where scientific evidence and data are inadequate and viewpoints differ, the Working Group included in this report different perspectives that are not yet resolved.

During the development of the 2020 Report, significant changes continued to occur within the ecosystem of Lyme disease and other tick-borne diseases and conditions as the footprint of tick-borne diseases and conditions expands across the nation. In addition to Working Group members, Federal agencies and the public actively engaged in the exchange of information with the Tick-Borne Disease Working Group and their input was a critical part of this report across areas including:

- Causes
- Prevention
- Treatment
- Surveillance
- Diagnosis
- Diagnostics
- Duration of Illness
- Intervention
- Gaps in Tick-Borne Disease Research

The 2020 Report was developed during an unprecedented global pandemic, which impacted patients with Lyme disease and other tick-borne diseases and conditions. The Tick-Borne Disease Working Group recognized that there might be lessons learned from the global response to the pandemic that could be helpful to the Lyme disease and other tick-borne diseases and conditions community in the future.

Today, one certainty is that the public needs support to address Lyme disease and other tick-borne diseases and conditions. The 2020 Report provides recommendations to that end. As part of a six-year process required by *the 21st Century Cure Act*, the forthcoming 2022 Tick-Borne Disease Working Group will develop a third report and make additional recommendations.

Appendices

Appendix A. Tick-Borne Disease Working Group

Dozens of individuals participated in the Tick-Borne Disease Working Group process, either directly or indirectly contributing to this 2020 report. The Working Group expresses their gratitude to the many members of the public—from across all sectors—who shared their expertise, stories, and recommendations to help improve the quality of the report. Additionally, a special thanks to subcommittee members of the Tick-Borne Disease Working Group who gave so generously of their time.

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CDR Todd Myers, PhD, HCLD (ABB), MB (ASCP) (Alternate to Estella Jones)
Office of Counterterrorism and Emerging Threats, Office of the Chief Scientist, Office of the Commissioner, U.S. Food and Drug Administration, U.S. Department of Health and Human Services

David N. Gaines, PhD
Public Health Entomologist, Virginia Department of Health

Hayley Yaglom, MS, MPH
One Health Genomic Epidemiologist, Translational Genomics Research Institute

Karen Bloch, MD, MPH, FIDSA, FACP
Associate Professor of Medicine (Infectious Disease) and Health Policy, Vanderbilt University Medical Center

Vance Fowler, MD
Professor of Medicine, Duke University

Christopher D. Paddock, MD, MPHTM
Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention

Lucas Blanton, MD
Assistant Professor, Department of Internal Medicine, University of Texas Medical Branch at Galveston

Christina M. Farris, PhD
Viral and Rickettsial Diseases Department, Naval Medical Research Center (*Resigned before the subcommittee's 8th meeting on October 22, 2019*)

Tony Galbo
Patient Perspectives and Advocacy

Tick Biology, Ecology, and Control Subcommittee

Kevin Macaluso, MS, PhD (Co-Chair)
Locke Distinguished Chair, Chair of Microbiology and Immunology, College of Medicine, University of South Alabama

Adalberto (Beto) A. Pérez de León, DVM, MS, PhD (Co-Chair)
Director, San Joaquin Valley Agricultural Sciences Center, U.S. Department of Agriculture - Agricultural Research Service

Jill Auerbach
Hudson Valley Lyme Disease Association (*Resigned on July 23, 2019*)

Tracy (Trey) Cahill
Public Health Analyst, Location Intelligence (GIS), Health Regulation & Licensing Administration, DC Health

Neeta Connally, PhD, MSPH
Associate Professor, Tick-borne Disease Prevention Laboratory, Western Connecticut State University

Maria Diuk-Wasser, PhD
Associate Professor and Principal Investigator, Eco-Epidemiology Lab, Department of Ecology, Evolution, and Environmental Biology, Columbia University

Lars Eisen, PhD
Research Entomologist, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention

Dina Fonseca, PhD
Professor and Director of the Center for Vector Biology, Department of Entomology, Rutgers, The State University of New Jersey (*Resigned on September 12, 2019*)

Howard Ginsberg, PhD
Research Ecologist, U.S. Geological Survey Patuxent Wildlife Research Center, Coastal Field Station, University of Rhode Island

Lonnie Marcum, PT, BSHCA
Physical Therapist; Health and Science Writer for LymeDisease.org

R. Michael Roe, PhD
William Neal Reynolds Distinguished Professor, Department of Entomology, North Carolina State University

Robert (Bob) Sabatino
Founder and Executive Director, Lyme Society, Inc.

Daniel Sonenshine, PhD
Eminent Professor of Biological Science, Old Dominion University; Guest Researcher, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Disease, National Institutes of Health

Kirby C. Stafford III, PhD
Chief Entomologist, Department of Entomology, Center for Vector Biology and Zoonotic Diseases, NE Regional Center for Excellence in Vector-Borne Diseases, The Connecticut Agricultural Experiment Station

Pete D. Teel, PhD
Regents Professor and Interim Department Head, Department of Entomology, Texas A&M University

Stephen Wikel, PhD
Professor and Chair Emeritus of Medical Sciences, St. Vincent's Medical Center, Quinnipiac University

Training, Education, Access to Care, and Reimbursement Subcommittee

Patricia (Pat) V. Smith, BA (Co-Chair)
President, Lyme Disease Association, Inc.; CDMRP Programmatic Panel Member

CDR Rebecca Bunnell, MPAS, PA-C (Co-Chair)
Special Assistant, Office of the Assistant Secretary for Financial Resources, U.S. Department of Health and Human Services

Elizabeth Maloney, MD (Co-Chair)
President, Partnership for Tick-Borne Diseases Education

Megan DuLaney, MS
Senior Interagency Liaison, Henry M. Jackson Foundation for the Advancement of Military Medicine in support of DoD and Center for Health Engagement, Uniformed Services University for the Health Sciences

Doug Fearn
President, Lyme Disease Association of Southeastern Pennsylvania, Inc.

Lorraine Johnson, JD, MBA
CEO, LymeDisease.org; Principal investigator, MyLymeData

Sheila M. Statlender, PhD
Clinical Psychologist, Private Practice

Topic Development *ad hoc* Subcommittees

Here are the volunteers and the three questions to which the Working Group decided to seek answers through literature reviews.

1. What are the causes of the increases in tick-borne diseases in the United States?

Adalberto (Beto) A. Pérez de León, DVM, MS, PhD
Director, San Joaquin Valley Agricultural Sciences Center, U.S. Department of Agriculture - Agricultural Research Service

Robert (Bob) Sabatino
Founder and Executive Director, Lyme Society, Inc.

2. What are the direct diagnostic tests available for tick-borne diseases, and what are the current states of the tests?

Charles Benjamin (Ben) Beard, PhD
Deputy Director, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention

Leigh Ann Soltysiak, MS
Integrated Marketing Communications, Northwestern University; Founder, Silverleaf Consulting, LLC; Adjunct Professor, "Entrepreneurial Thinking," Stevens Institute of Technology

3. What are the causes of the persistent symptoms of Lyme disease?

CDR Rebecca Bunnell, MPAS, PA-C
Special Assistant, Office of the Assistant Secretary for Financial Resources, U.S. Department of Health and Human Services

Sam T. Donta, MD
Professor of Medicine (retired); Consultant, Infectious Diseases, Falmouth Hospital, Falmouth, MA

Appendix C. Acronyms and Abbreviations

Acronym/Abbreviation	Definition
AGS	Alpha-gal Syndrome
AHRQ	Agency for Healthcare Research and Quality
AV	Atrioventricular
CDC	Centers for Disease Control and Prevention
CME	Continuing medical education
CMS	Centers for Medicare & Medicaid Services
CSTE	Council of State and Territorial Epidemiologists
DFO	Designated federal officer
DoD	U.S. Department of Defense
ELISA	Enzyme Linked Immunosorbent Assay
EM	Erythema migrans
EMR	Electronic medical record
FACA	Federal Advisory Committee Act
FDA	U.S. Food and Drug Administration
HGA	Human granulocytic anaplasmosis
HME	Human monocytic ehrlichiosis
HHS	U.S. Department of Health and Human Services
IDN	Integrated Delivery Network
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILADS	International Lyme and Associated Diseases Society
MMWR	Morbidity and Mortality Weekly Report
NAAT	Nucleic acid amplification test
NIH	National Institutes of Health

Acronym/Abbreviation	Definition
OASH	HHS Office of the Assistant Secretary for Health
PCORI	Patient-Centered Outcomes Research Institute
PET	Positron emission tomography
SFG	Spotted fever group
SPECT	Single-photon emission computed tomography
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
WHO	World Health Organization
WNV	West Nile Virus

Appendix D. *21st Century Cures Act*

The *21st Century Cures Act*, enacted in December 2016, authorizes the HHS Secretary to establish a Tick-Borne Disease Working Group to serve as a Federal Advisory Committee. The Working Group is to comprise federal and public members with diverse disciplines and views pertaining to tick-borne diseases. The Act charges the Working Group to provide a report to Congress and the HHS Secretary on its findings and any recommendations every two years. Working Group responsibilities include a review of ongoing research and resulting advances; Federal epidemiological and research efforts; and identification of research gaps. The *21st Century Cures Act*, Section 2062 Tick-Borne Diseases, is provided below. The legislation is available in its entirety at https://www.congress.gov/bill/114th-congress/house-bill/34/text.

SEC. 2062. TICK-BORNE DISEASES.

(a) IN GENERAL. The Secretary of Health and Human Services (referred to in this section as ''the Secretary'') shall continue to conduct or support epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tick-borne diseases.

(b) REPORTS. The Secretary shall ensure that each triennial report under section 403 of the Public Health Service Act (42 U.S.C. 283) (as amended by section 2032) includes information on actions undertaken by the National Institutes of Health to carry out subsection (a) with respect to tick-borne diseases.

(c) TICK-BORNE DISEASES WORKING GROUP.

(1) ESTABLISHMENT. The Secretary shall establish a working group, to be known as the Tick-Borne Disease Working Group (referred to in this section as the ''Working Group''),comprised of representatives of appropriate Federal agencies and other non-Federal entities, to provide expertise and to review all efforts within the Department of Health and Human Services related to all tick-borne diseases, to help ensure interagency coordination and minimize overlap, and to examine research priorities.

(2) RESPONSIBILITIES. The working group shall

(A) Not later than 2 years after the date of enactment of this Act, develop or update a summary of

(i) Ongoing tick-borne disease research, including research related to causes, prevention, treatment, surveillance, diagnosis, diagnostics, duration of illness, and intervention for individuals with tick-borne diseases;

(ii) Advances made pursuant to such research;

(iii) Federal activities related to tick-borne diseases, including

(I) Epidemiological activities related to tick-borne diseases; and

(II) Basic, clinical, and translational tick-borne disease research related to the pathogenesis, prevention, diagnosis, and treatment of tick-borne diseases;

(iv) Gaps in tick-borne disease research described in clause (iii)(II);

(v) The Working Group's meetings required under paragraph (4); and

(vi) The comments received by the Working Group;

(B) Make recommendations to the Secretary regarding any appropriate changes or improvements to such activities and research; and

(C) Solicit input from States, localities, and nongovernmental entities, including organizations representing patients, health care providers, researchers, and industry regarding scientific advances, research questions, surveillance activities, and emerging strains in species of pathogenic organisms.

(3) MEMBERSHIP. The members of the working group shall represent a diversity of scientific disciplines and views and shall be composed of the following members:

(A) FEDERAL MEMBERS. Seven Federal members, consisting of one or more representatives of each of the following:

(i) The Office of the Assistant Secretary for Health.

(ii) The Food and Drug Administration.

(iii) The Centers for Disease Control and Prevention.

(iv) The National Institutes of Health.

(v) Such other agencies and offices of the Department of Health and Human Services as the Secretary determines appropriate.

(B) NON–FEDERAL PUBLIC MEMBERS. Seven non–Federal public members, consisting of representatives of the following categories:

(i) Physicians and other medical providers with experience in diagnosing and treating tick-borne diseases.

(ii) Scientists or researchers with expertise.

(iii) Patients and their family members.

(iv) Nonprofit organizations that advocate for patients with respect to tick-borne diseases.

(v) Other individuals whose expertise is determined by the Secretary to be beneficial to the functioning of the Working Group.

(4) MEETINGS. The Working Group shall meet not less than twice each year.

(5) REPORTING. Not later than 2 years after the date of enactment of this Act, and every 2 years thereafter until termination of the Working Group pursuant to paragraph (7), the Working Group shall

(A) Submit a report on its activities under paragraph (2)(A) and any recommendations under paragraph (2)(B) to the Secretary, the Committee on Energy and Commerce of the House of Representatives, and the Committee on Health, Education, Labor, and Pensions of the Senate; and

(B) Make such report publicly available on the Internet website of the Department of Health and Human Services.

(6) APPLICABILITY OF FACA. The Working Group shall be treated as an advisory committee subject to the Federal Advisory Committee Act (5 U.S.C. App.).

(7) SUNSET. The Working Group under this section shall terminate 6 years after the date of enactment of this Act.

Appendix E. Working Group Charter

The Charter defines how the Working Group will be structured and function in response to the charge provided by the *21st Century Cures Act* (Appendix D). and is renewed every two years in accordance with Federal advisory committee guidelines. The current charter expires August 10, 2021.

Tick-borne Disease Working Group

Authority

The Tick-borne Disease Working Group (hereafter referred to as the Working Group) is required under Section 2062 of the *21st Century Cures Act*. The Working Group is governed by the provisions of the *Federal Advisory Committee Act* (FACA), Public Law 92-463, as amended (5 U.S.C. App), which sets forth standards for the formation and use of advisory committees.

Objectives and Scope of Activities

The Secretary of Health and Human Services (Secretary) is responsible for ensuring the conduct of or support for epidemiological, basic, translational, and clinical research related to vector-borne diseases, including tick-borne diseases. The Working Group will provide expertise and review all efforts within the Department of Health and Human Services related to all tick-borne diseases, to help ensure interagency coordination and minimize overlap, and to examine research priorities.

Description of Duties

The Working Group shall have the following responsibilities:

(A) Not later than two years after the date of enactment of the authorizing legislation, develop or update a summary of:

(1) Ongoing tick-borne disease research, including research related to causes, prevention, treatment, surveillance, diagnosis, diagnostics, duration of illness, and intervention for individuals with tick-borne diseases;

(2) Advances made pursuant to such research;

(3) Federal activities related to tick-borne diseases, including:

(a) Epidemiological activities related to tick-borne diseases; and

(b) Basic, clinical, and translational tick-borne disease research related to the pathogenesis, prevention, diagnosis, and treatment of tick-borne diseases.

(4) Gaps in tick-borne disease research described in clause 3b;

(5) The Working Group's meetings; and

(6) The comments received by the Working Group.

(B) Make recommendations to the Secretary regarding any appropriate changes or improvement to such activities and research; and

(C) Solicit input from States, localities, and non-governmental entities, including organizations representing patients, health care providers, researchers, and industry regarding scientific advances, research questions, surveillance activities, and emerging strains in species of pathogenic organisms.

Agency or Official to Whom the Working Group Reports

The Working Group will provide recommendations to the Secretary.

Not later than two years after the date of enactment of the authorizing legislation (December 13, 2016) and every two years thereafter until the Working Group is terminated pursuant to the stipulations of the authorizing legislation, the Working Group shall:

(A) Submit a report on its activities and any recommendations, as stipulated under the Description of Duties (A) and (B), to the Secretary, the Committee on Energy and Commerce of the House of Representatives, and the Committee on Health, Education, Labor, and Pensions of the Senate; and

(B) Make such report publicly available on the Internet website of the Department of Health and Human Services.

Support

Management and support services for the Working Group's activities will be provided by staff from within the Office of the Assistant Secretary for Health (OASH). OASH is a staff division within the Office of the Secretary in the Department of Health and Human Services.

Estimated Annual Operating Costs and Staff Years

Estimated annual cost for operating the Working Group, including compensation and travel expenses for members, but excluding staff support, is $237,000. Estimated person years of staff support required is 2.0, at an estimated annual cost of $250,560.

Designated Federal Officer (DFO)

The ASH will select the Designated Federal Officer (DFO) from among full-time or permanent part-time staff within OASH, who have knowledge of the subject matter and skills and experience necessary to manage the Working Group. The ASH may appoint an Alternate DFO who will carry out these duties

in the event that the appointed DFO cannot fulfill the assigned responsibilities for the Working Group. In the absence of the appointed DFO or Alternate DFO, the ASH will temporarily appoint one or more permanent full-time or part-time program staff to carry out the assigned duties.

The DFO will schedule and approve all meetings of the Working Group and any subcommittees that may be established by the Working Group. The DFO will prepare and approve all meeting agendas. The DFO may collaborate with the Working Group Chair in this activity, and when deemed appropriate, with chairs of any existing subcommittees that have been established by the Working Group. The DFO, Alternate DFO, or designee will attend all meetings of the Working Group and all meetings of any subcommittees that have been established to assist the Working Group. The DFO has authority to adjourn meetings, when it is determined to be in the public interest, and the DFO can be directed by the Secretary or designee to chair meetings of the Working Group.

Estimated Number and Frequency of Meetings

The Working Group will meet not less than twice a year, and these may be conducted by teleconference or video conference at the discretion of the ASH. The meetings will be open to the public, except as determined otherwise by the Secretary, or other official to whom authority has been delegated, in accordance with the guidelines under *Government in the Sunshine Act*, 5 U.S.C. 552b(c). Notice of all meetings will be provided to the public in accordance with the FACA. Meetings will be conducted and records of the proceedings will be kept, as required by applicable laws and departmental policies. A quorum is required for the Working Group to meet to conduct business. A quorum will consist of a majority of the Working Group's voting members.

When the Secretary or designee determines that a meeting will be closed or partially closed to the public, in accordance with stipulations of *Government in the Sunshine Act*, 5 U.S.C. 552b(c), then a report will be prepared by the DFO that includes, at a minimum, a list of members and their business addresses, the Working Group's functions, date and place of the meeting, and a summary of the Working Group's activities and recommendations made during the fiscal year. A copy of the report will be provided to the Department Committee Management Officer.

Duration

Establishment of the Working Group was mandated under Section 2602 of the *21st Century Cures Act*. The Working Group will operate pursuant to the stipulations in the authorizing legislation.

Termination

Unless extended by Congress, the Working Group will be terminated (on December 13, 2022) six years after the date of enactment of the authorizing legislation. Unless renewed by appropriate action, the charter for the Working Group will expire two years from the date it is filed.

Membership and Designation

The Working Group will consist of 14 voting members, including the Chair, who represent diverse scientific disciplines and views. The composition will include seven Federal members and seven non-Federal public members. The Federal members will consist of one or more representatives of each of the following: OASH, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the National Institutes of Health. The non-Federal public members will consist of representatives of the following categories: physicians and other medical providers with experience in diagnosing and treating tick-borne diseases; scientists or researchers with expertise; patients and their family members; nonprofit organizations that advocate for patients with respect to tick-borne diseases. One or more of the non-Federal public members will be selected by the Secretary to serve as the Chair, Vice Chair, and/or Co-Chairs. Individuals who are appointed to represent Federal entities will be classified as regular government employees. The non-Federal public members will be classified as special government employees. Invitations of membership will be extended to other agencies and offices of the Department of Health and Human Services and other individuals as determined by the Secretary to be appropriate and beneficial to the functioning of the Working Group.

The Federal members will be appointed to serve for the duration of time that the Working Group is authorized to operate. Participation of the appointed Federal members will be at the discretion of the respective agency head. The non-Federal public members will be invited to serve as special government employees for overlapping terms of up to four years. Any non-Federal public member who is appointed to fill the vacancy of an unexpired term will be appointed to serve for the remainder of that term. A non-Federal public member may serve after the expiration of their term until their successor has taken office, but no longer than 180 days.

Pursuant to advance written agreement, non-Federal public members of the Working Group will receive no stipend for the advisory service that they render as members of the Working Group. However, non-Federal public members will receive per diem and reimbursement for travel expenses incurred in relation to performing duties for the Working Group, as authorized by law under 5 U.S.C. 5703 for persons who are employed intermittently to perform services for the Federal government and in accordance with Federal travel regulations.

Subcommittees

In carrying out its function, the Working Group may establish subcommittees composed of members of the Working Group, as well as other individuals who have expertise and knowledge about the topics and issues that are pertinent to the mission of the Working Group. The established subcommittee may consider issues in accordance with the mission of the Working Group, and will, as appropriate, make recommendations and/or reports to the Working Group for consideration. Recommendations and/or reports of the subcommittee that are provided to the Working Group will be discussed at an open public meeting that is held by the Working Group. No established subcommittee of the Working Group may report directly to the Secretary or another Federal official unless there is specific statutory authority for such reporting. The Department Committee Management Officer will be notified upon

establishment of each subcommittee, and will be given information regarding its name, membership, function, cost, and estimated frequency of meetings.

Recordkeeping

Records of the Working Group and any established subcommittees will be handled in accordance with the General Records Schedule 6.2, Federal Advisory Committee Records or other approved agency records disposition schedule. Applicable records will be made available to the public for inspection and copying, subject to the *Freedom of Information Act*, 5 U.S.C. 552.

Approved:

August 7, 2019

Alex M. Azar II
Secretary of Health and Human Services

Appendix F. Federal Inventory Survey

Inventory of HHS Tick-Borne Disease Projects and Activities

Summary: The Tick-Borne Disease Working Group, which is housed at the Office of the Assistant Secretary for Health at HHS, is conducting an inventory of all funded and unfunded activities related to Lyme or other tick-borne diseases. This information will inform the Tick-borne Disease Working Group Report to Congress, which will be delivered to Congress in December 2020. This is the second Congressional report that is specific to tick-borne diseases. This report provides us the opportunity to present the importance and urgency of the work we are doing related to tick-borne diseases.

Request: Please complete this survey by **December 13, 2019**. If there are data elements that cannot be provided in this timeframe, we request that you submit partial data by the deadline along with an explanation on why you cannot provide the data and the date by which we can expect the completed; data sets. You will have an opportunity to review and update your information as we run through the compilation, edit and review process. While we recognize that many of you have been working in, and advocating for tick-borne diseases for decades, **for the purposes of reporting, we are interested only in activities or projects that were funded in FY17 or later.**

Questions: If you have any questions, please contact Chinedu Okeke, MD, MPH-TM, Senior Policy Advisor (Medical Officer), Office of the Assistant Secretary for Health, Department Health and Human Services or Allison Petkoff, ORISE Fellow.

Background: The 21st Century Cures Act establishes the Tick-Borne Disease Working Group and makes it responsible for providing subject matter expertise, to identify priorities, review the Federal response, help ensure interagency coordination and minimize overlap, identify gaps, and provide recommendations to improve these efforts.

The purpose of the Inventory of HHS Tick-Borne Disease Projects and Activities is to provide a summary of HHS activities related to tick-borne diseases for the second Report to Congress of the Tick-Borne Disease Working Group in December 2020. This report will include:

1. What the agencies are doing and spending each year with regard to tick-borne diseases;
2. Epidemiological activities related to tick-borne diseases;
3. Basic, clinical, and translational tick-borne disease research related to the pathogenesis, prevention, diagnosis, and treatment of tick-borne diseases; and
4. Gaps in tick-borne disease research described above.

For the purposes of reporting, this inventory is being grouped into three focus areas: Agency Overview (Focus Area 1), Intramural Activities (Focus Area 2), and Extramural Activities (Focus Area 3).

Focus Area I: Agency Overview

Complete each section to provide information on the resources provided by your agency or office that support improvements in the nation's ability to respond to tick-borne diseases.

(A) Check a box for each of the categories relevant to your agency projects or activities involving tick-borne diseases. Check as many boxes as apply.

- ☐ Basic Research
- ☐ Capacity Building and Technical Assistance
- ☐ Development of diagnostic or treatment protocols
- ☐ Education
- ☐ Epidemiology
- ☐ Medical Care and Treatment
- ☐ Mental Health Services
- ☐ Mental Health Support Groups
- ☐ Other_____
- ☐ Other Supportive Services
- ☐ Prevention
- ☐ Policy Development
- ☐ Regulation
- ☐ Research-Co-infections
- ☐ Research-Diagnostics
- ☐ Research-Human Translational
- ☐ Research-Pathogenesis
- ☐ Research-Treatment
- ☐ Research-Treatment
- ☐ Research-Vaccine
- ☐ Research-Vector Control
- ☐ Surveillance-Human
- ☐ Surveillance-Vector
- ☐ Testing Programs
- ☐ Training
- ☐ Vector Control
- ☐ Vector Ecology

(B) The categories below represent subcommittees of the Tick-Borne Disease Working Group. Check a box to indicate the relevance of your agency projects and activities to these subcommittees. Check as many boxes as apply.

- ☐ Access to Care Services and Support to Patients
- ☐ Disease Vectors, Surveillance and Prevention
- ☐ Other Tick-Borne Diseases and Co-Infections
- ☐ Pathogenesis, Transmission, and Treatment
- ☐ Testing and Diagnostics
- ☐ Vaccine and Therapeutics

(C) Check a box for each of the tick-borne diseases addressed by your agency projects or activities. Check as many boxes as apply.

Bacterial Infections

- ☐ Anaplasma
- ☐ Bartonella
- ☐ Ehrlichia
- ☐ Lyme Disease (Borrelia burgdorferi)
- ☐ Master's disease/stari
- ☐ Mycoplasma
- ☐ Others (Specify and list all):_____
- ☐ Relapsing Fever Borrelia (Borrelia miyamotoi, hermsii)
- ☐ Rickettsia (Q-fever, Rocky Mountain Spotted Fever, Typhus)
- ☐ Sensu Lato spp.
- ☐ Tularemia

Parasitic Infections

- ☐ Babesiosis (duncani/microti)
- ☐ Filariasis (tick-borne)
- ☐ Others (Specify and list all):_____

Tick-Borne Viral Infections

- ☐ Bourbon Disease
- ☐ Colorado Tick Fever
- ☐ DTV/Powassan Disease
- ☐ Heartland Disease
- ☐ Others (Specify and list all):_____

Co-Infection with Any Combination of Tick-Borne Diseases

- ☐ No
- ☐ Yes

Alpha Gal Allergy or Other Tick-Borne-Disorders and Associated Diseases

- ☐ Alpha Gal
- ☐ Others (Specify and list all):_____

(D) Complete information in the table below. Be as descriptive as possible. Respond N/A if not applicable.

Definition: Tick-borne diseases are all those listed in section C of this inventory.

GENERAL FUNDING AND REPORTING	
1. Name of Agency or office	
2. FY18 federal funding for your agency or office	
3. FY18 federal funding for tick-borne diseases (if available)	
4. FY17 federal funding for tick-borne diseases	

GENERAL FUNDING AND REPORTING (continued)	
5. FY10-16 federal funding for tick-borne diseases (delineated by year)	
6. In which year did your agency or office first begin funding tick-borne activities or projects (that you can provide data for)?	
7. How often do you report on expenditures that are specific to tick-borne diseases?	(Multiple Choice)- annually, semi-annually, quarterly, monthly, other [specify]
8. Do you include spending or budget summaries in reports specific to tick-borne disease projects or activities?	Yes/No
9. If no, what prevents your agency or office from reporting spending on tick-borne disease projects or activities?	
STAFFING	
10. Number of full time employees (FTEs) supported with these funds budgeted for tick-borne diseases	
11. Number of additional FTEs dedicated to tick-borne disease activities	
12. Number of fellows, contractors, or other support staff (not included above) supported with these funds	
13. Which organizational units in your Agency or office manage your tick-borne disease projects and activities?	
14. Which one of these (if any) has primary oversight of your tick-borne diseases portfolio?	
15. Name and contact information of Director or Chief with primary oversight. Include email and phone number.	
16. Which organizational unit at your Agency or office is responsible for establishing diagnostic or treatment protocols?	

STRATEGIC PLANNING AND REPORTING	
17. Does your agency or office have a strategic plan for addressing tick-borne diseases? If yes, please include a link to the document or attach a file.	Yes/No
18. If no, does your agency or office address tick-borne illnesses in your agency strategic plan or other priority setting documents? If yes, please include a link to the document or attach a file.	Yes/No
19. What are the future opportunities for improving efficiency, effectiveness, and/or impact of your activities for tick-borne diseases	
20. What unmet needs have been identified through your agency or office's work on tick-borne diseases?	
21. Does your agency or office engage patients, the public and other stakeholders in planning activities and obtaining feedback on activities?	
22. If yes, how does your agency or office engage patients, the public and other stakeholders in planning activities?	(Multiple Choice)- Surveys, town-hall meetings, focus groups, other [specify]
23. How does feedback from patients and the public inform the development of programs and activities?	

MATERIAL DEVELOPMENT, GUIDELINES & PROTOCOLS	
24. Since 2010 or in the last year (specify), what educational or training tools, toolkits, products or resources have been developed by your agency or office for tick-borne diseases? Provide links to the material where possible.	
25. Since 2010 or in the last year (specify), what publications has agency staff authored or co-authored about tick-borne diseases. Include surveillance or agency authored reports. Provide links where possible.	
26. What guidelines or medical protocols does your agency or office use for diagnosis and treatment of tick-borne diseases that are contracted in the U.S.? Provide links or attachments where possible.	
27. How many people have been diagnosed with Lyme or another tick-borne disease in the U.S.?	
28. How many people diagnosed with Lyme or another tick-borne disease in the U.S. were treated and remain asymptomatic after treatment?	
29. What guidelines or medical protocols does your agency or office use for diagnosis and treatment of tick-borne diseases that are contracted abroad? Provide links or attachments where possible.	
30. How many people have contracted Lyme or another tick-borne disease abroad?	

Focus Area II: Intramural Projects or Activities

For each intramural project or activity, complete each section to provide information on the projects and activities that are conducted to support improvements in the nation's ability to respond to tick-borne diseases. Most of the funding for intramural projects and activities stay within the agency. Examples of intramural projects and activities include, but are not limited to, development of policies and procedures; regulations; guidance and guidelines; research; diagnostic and treatment protocols; and website content.

(1) How many intramural projects related to tick-borne diseases does your office or agency currently manage?

(2) List the name of each intramural project or activity your agency or office currently has related to tick-borne diseases. Add additional lines if necessary.

(3) List the name of each previously funded intramural project or activity your agency or office managed since 2010. Add additional lines if necessary

(4) Provide the information requested in sections A, B, C, and D below for each of your intramural projects or activities (since 2010) related to tick-borne diseases. **Make sure to copy these sections as many times as necessary to cover this information for each individual intramural project or activity.**

[Insert Project or Activity Name]

(A) Check a box for each of the categories relevant to this project or activity involving tick-borne diseases. Check as many boxes as apply.

- ☐ Basic Research
- ☐ Capacity Building and Technical Assistance
- ☐ Development of Diagnostic or Treatment Protocols
- ☐ Education

- ☐ Epidemiology
- ☐ Medical Care and Treatment
- ☐ Mental Health Services
- ☐ Mental Health Support Groups
- ☐ Other_____
- ☐ Other Supportive Services
- ☐ Prevention
- ☐ Policy Development
- ☐ Regulation
- ☐ Research-Co-infections
- ☐ Research-Diagnostics
- ☐ Research-Human Translational
- ☐ Research-Pathogenesis
- ☐ Research-Treatment
- ☐ Research-Treatment
- ☐ Research-Vaccine
- ☐ Research-Vector Control
- ☐ Surveillance-Human
- ☐ Surveillance-Vector
- ☐ Testing Programs
- ☐ Training
- ☐ Vector Control
- ☐ Vector Ecology

(B) The categories below represent subcommittees of the Tick-Borne Disease Working Group. Check a box to indicate the relevance of your agency projects and activities to these subcommittees. Check as many boxes as apply.

- ☐ Access to Care Services and Support to Patients
- ☐ Disease Vectors, Surveillance and Prevention
- ☐ Other Tick-Borne Diseases and Co-Infections
- ☐ Pathogenesis, Transmission, and Treatment
- ☐ Testing and Diagnostics
- ☐ Vaccine and Therapeutics

(C) Check a box for each of the tick-borne diseases addressed this project or activity. Check as many boxes as apply.

Bacterial Infections

- ☐ Anaplasma
- ☐ Bartonella
- ☐ Ehrlichia
- ☐ Lyme Disease (Borrelia burgdorferi)
- ☐ Master's disease/stari
- ☐ Mycoplasma
- ☐ Others (Specify and list all):_____
- ☐ Relapsing Fever Borrelia (Borrelia miyamotoi, hermsii)
- ☐ Rickettsia (Q-fever, Rocky Mountain Spotted Fever, Typhus)
- ☐ Sensu Lato spp.
- ☐ Tularemia

Parasitic Infections

- ☐ Babesiosis (duncani/microti)
- ☐ Filariasis (tick-borne)
- ☐ Others (Specify and list all):_____

Tick-Borne Viral Infections

- ☐ Bourbon Disease
- ☐ Heartland Disease
- ☐ Colorado Tick Fever
- ☐ Others (Specify and list all):_____
- ☐ DTV/Powassan Disease

Co-Infection with Any Combination of Tick-Borne Diseases

- ☐ No
- ☐ Yes

Alpha Gal Allergy or Other Tick-Borne-Disorders and Associated Diseases

- ☐ Alpha Gal
- ☐ Others (Specify and list all):_____

(D) Complete information in the table below for the project or activity listed above. Be as descriptive as possible.

1.	Purpose of project or activity	
2.	Is this project/activity currently funded?	Yes/No
3.	If yes, give year project started (FY)	
4.	If no, give years project started and ended	FY started FY ended
5.	Top three (3) project/activity results	Result 1: Result 2: Result 3:
6.	Total project period (FY-FY)	
7.	Total project/activity funding in FY17 (if applicable)	
8.	What type of entities are funded (i.e. CBOs, Health Centers, Universities, etc.)?	
9.	In which states are grantees located?	
10.	Number of full time employees (FTEs) supported with these funds	

11. Number of fellows, contractors, or other support staff (not included above) supported with these funds
12. Organizational unit responsible for this project or activity (i.e. Division, Bureau, Branch)?
13. Project Person of Contact (POC). Include email address and phone number
14. Links to website or other digital content
15. List of peer reviewed publications produced
16. List of patents generated

Focus Area III: Extramural Projects or Activities

For each extramural project or activity, complete each section to provide information on the projects and activities that are conducted to support improvements in the nation's ability to respond to tick-borne diseases. Most of the funding for these projects and activities are provided to grantees outside of the agency or office. Examples of extramural projects and activities include, but are not limited to, research; projects funded through an FOA process; projects managed by outside entities such as CBOs, state and city health departments, community health centers, etc.

(1) How many extramural projects related to tick-borne diseases does your office or agency currently manage?

(2) List the name of each extramural project or activity your agency or office currently has related to tick-borne diseases. Add additional lines if necessary.

(3) List the name of each previously funded extramural project or activity your agency or office managed since 2010. Add additional lines if necessary

(4) Provide the information requested in sections A, B, C, and D for each of your active extramural projects or activities related to tick-borne diseases. **Make sure to copy these sections as many times as necessary to cover this information for each individual extramural project or activity.**

[Insert Project or Activity Name]

(A) Check a box for each of the categories relevant to this project or activity involving tick-borne diseases. Check as many boxes as apply.

- ☐ Basic Research
- ☐ Capacity Building and Technical Assistance
- ☐ Development of diagnostic or treatment protocols
- ☐ Education
- ☐ Epidemiology
- ☐ Medical Care and Treatment
- ☐ Mental Health Support Groups
- ☐ Other_____
- ☐ Other Supportive Services
- ☐ Prevention
- ☐ Policy Development
- ☐ Regulation
- ☐ Research-Co-infections
- ☐ Research-Diagnostics
- ☐ Research-Human Translational
- ☐ Research-Pathogenesis
- ☐ Research-Treatment
- ☐ Research-Vaccine
- ☐ Research-Vector Control
- ☐ Surveillance-Human
- ☐ Surveillance-Vector
- ☐ Testing Programs
- ☐ Training
- ☐ Vector Control
- ☐ Vector Ecology

(B) The categories below represent subcommittees of the Tick-Borne Disease Working Group. Check a box to indicate the relevance of your agency projects and activities to these subcommittees. Check as many boxes as apply.

- ☐ Access to Care Services and Support to Patients
- ☐ Disease Vectors, Surveillance and Prevention
- ☐ Other Tick-Borne Diseases and Co-Infections
- ☐ Pathogenesis, Transmission, and Treatment
- ☐ Testing and Diagnostics
- ☐ Vaccine and Therapeutics

(C) Check a box for each of the tick-borne diseases addressed by this project or activity. Check as many boxes as apply.

Bacterial Infections

- ☐ Anaplasma
- ☐ Bartonella
- ☐ Ehrlichia
- ☐ Lyme Disease (Borrelia burgdorferi)
- ☐ Master's disease/stari
- ☐ Mycoplasma
- ☐ Others (Specify and list all):_____
- ☐ Relapsing Fever Borrelia (Borrelia miyamotoi, hermsii)
- ☐ Rickettsia (Q-fever, Rocky Mountain Spotted Fever, Typhus)
- ☐ Sensu Lato spp.
- ☐ Tularemia

Parasitic Infections

- ☐ Babesiosis (duncani/microti)
- ☐ Filariasis (tick-borne)
- ☐ Others (Specify and list all):_____

Tick-Borne Viral Infections

- ☐ Bourbon Disease
- ☐ Heartland Disease
- ☐ Colorado Tick Fever
- ☐ Others (Specify and list all):_____
- ☐ DTV/Powassan Disease

Co-Infection with Any Combination of Tick-Borne Diseases

- ☐ No
- ☐ Yes

Alpha Gal Allergy or Other Tick-Borne-Disorders and Associated Diseases

- ☐ Alpha Gal
- ☐ Others (Specify and list all):_____

(D) Complete information in the table below for the project or activity listed above. Be as descriptive as possible.

1.	Purpose of project or activity	
2.	Is this project/activity currently funded?	Yes/No
3.	If yes, give year project started (FY)	
4.	If no, give years project started and ended	FY started FY ended
5.	Top three (3) project/activity results	Result 1: Result 2: Result 3:

6. Total project period (FY-FY)
7. Total project/activity funding in FY17 (if applicable)
8. What type of entities are funded (i.e. CBOs, Health Centers, Universities, etc.)?
9. In which states are grantees located?
10. Number of full time employees (FTEs) supported with these funds
11. Number of fellows, contractors, or other support staff (not included above) supported with these funds
12. Organizational unit responsible for this project or activity (i.e. Division, Bureau, Branch)?
13. Project Person of Contact (POC). Include email address and phone number
14. Links to website or other digital content
15. List of peer reviewed publications produced
16. List of patents generated

Appendix G. References

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