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# Tick-Borne Disease Working Group



## 2018 Report to Congress (Draft)

Information and opinions in this report do not necessarily reflect the opinions 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

**T**ICK-BORNE DISEASES have rapidly become a serious and growing threat to public health in the United States. Despite many scientific unknowns, experts agree that the incidence and distribution of tick-borne diseases are increasing. Over the past 25 years, reports of Lyme disease have increased steadily with estimated annual cases exceeding 300,000. The number of U.S. counties now considered to be of high-incidence for Lyme disease has increased by more than 300% in the northeastern states and by approximately 250% in the north-central states. The Centers for Diseases Control and Prevention (CDC) currently recognizes 18 tick-borne pathogens in the United States. However, researchers and health care practitioners continue to discover emerging disease agents and new medical conditions associated with tick bites.

While most Lyme disease patients who are diagnosed and treated early can fully recover, 10 to 20% of patients suffer from persistent symptoms, which for some are chronic and disabling. Studies indicate that Lyme disease costs approximately \$1.3 billion each year in direct medical costs alone in the United States. A comprehensive understanding of the full economic and societal cost remains unknown. It is likely orders of magnitude higher and potentially a \$50- to \$100-billion-dollar problem for the United States, although more research is needed (Vanderhoof & Vanderhoof-Forschner, 1993; Zhang et al., 2006).

Prompt diagnosis and treatment of tick-borne diseases are crucial to prevent long-term

complications. Today, available diagnostic tests can be inaccurate and complex to interpret, especially during the earliest stage of infection when treatment is most effective. Unlike in other infectious disease settings, tests to directly measure the presence of the infecting organism, such as cultures or tissue biopsies, are not available for some tick-borne diseases such as Lyme disease. This leaves physicians without the tools needed to diagnose; and without an accurate diagnosis, it is challenging for physicians to provide early treatment.

Persistent symptoms after treatment of Lyme disease can be severe, yet their cause(s) remains unknown and debated. There are currently no uniformly accepted or validated treatment



# LYME DISEASE



Lyme disease has increased by more than **300%** in the northeastern states and by approximately **250%** in the north-central states.



options for patients with these chronic symptoms. As a result, uncertainty surrounding appropriate clinical care has led to polarization within the medical community, and patients are often left suffering in limbo without a clear path to illness resolution or even symptom management (Rebman et al., 2017). The lack of a clear path for treatment of persistent symptoms in some patients with Lyme disease and other tick-borne diseases not only amplifies patient suffering but also significantly increases health care costs.

This report outlines an integrated, multipronged approach to the growing public health challenges posed by tick-borne diseases in the United States. It contains seven main chapters, including Background and Methods, Epidemiology and Ecology, Prevention, Diagnosis, Treatment, Access to Care and Patient Outcomes, and Looking Forward. The Background and Methods chapter explains how the report was developed. The other chapters present the main challenges, key issues, and recommendations specific to the broader topics.

To understand tick-borne diseases, we need to first understand tick ecology, and how ticks transmit diseases. Due to the lack of a coordinated national surveillance program, currently there are significant gaps in information on local distribution of infection-causing ticks, especially in regions beyond the Northeast and Upper Midwest. Nationwide, standardized approaches for tick, animal, and human surveillance are needed to understand the geographic distribution of infectious ticks in order to understand the spread of disease and predict where people are at risk. Advanced technologies and systematic studies are also needed to rapidly identify new disease agents that pose emergent risks to public health, including to the blood supply. Given that seven new tick-borne pathogens have been shown to infect people in the United States since 2004, this is a priority.

Effective prevention relies on multipronged strategies. To reduce exposure to ticks, we need a comprehensive understanding of the biological drivers behind the continued spread of tick-

borne diseases, so that effective tick and infection control methods can be identified and validated. Need also exists for the transparent development of a safe, effective human vaccine to prevent Lyme disease, the most common of these illnesses. In the absence of effective strategies for controlling ticks and blocking the transmission of tick-borne pathogens, it is crucial to educate health care professionals and the public about tick-borne disease prevention, especially best practices for protection from tick bites. Outreach efforts to promote prevention and raise awareness among physicians and the public must be expanded at both the Federal and state level to ensure accurate, effective, and consistent messaging.

Clinical research priorities must include the development of new technologies and approaches to improve diagnosis of tick-borne diseases and monitor response to treatment. There is a critical need for sensitive and specific direct-pathogen detection strategies that are broad enough to cover multiple potential tick-borne pathogens. Understanding the etiology and pathogenesis of ongoing symptoms after initial treatment should be a clinical research priority. Investigations are also needed into the potential roles of immunologic responses, bacterial persistence, and coinfecting pathogens in order to design and test new therapies and, ultimately, improve outcomes and care for patients with ongoing symptoms.

Americans need help, yet progress has been hampered by a lack of attention at the Federal level and divisions within the field. The recommendations in this 2018 report of the Tick-Borne Disease Working Group represent a long-term investment in tackling the rise of tick-borne diseases in this country. However, immediate

changes are also required to help patients already suffering from tick-borne diseases; to protect them from discrimination; and to address the inflexible, inconsistent, and often unaffordable care that patients frequently encounter in the current health care system.

Increased Federal funding, prioritization, and leadership are needed to reverse the alarming trends associated with tick-borne diseases.

Despite several decades of research, prevention, and educational activities, Federal funding for tick-borne diseases is less per new case than that of other diseases. The U.S. National Institutes of Health (NIH) and CDC spend \$53,571 and \$14,054, respectively, per new case of HIV/AIDS, and \$82,308 and \$26,154 per new case of Hepatitis C virus, yet only \$90 and \$35 for each new case of Lyme disease. Federal funding for tick-borne disease today is orders of magnitude lower, compared to other public health threats, and it has failed to increase as the problem has grown.

It is also essential that funding and resources be allocated to support a comprehensive, interagency program to address the mounting challenges identified in this report. All research, prevention, and education initiatives should be inclusive of special populations such as children, who suffer disproportionately from tick-borne diseases. Patients whose lives continue to be disrupted by the lasting effects of these illnesses are counting on emerging scientific research, evidence-based policy, and the health care establishment—including the Federal Government with Congressional and Executive leadership—to provide solutions. We must act now.

**Figure 1: Federal Funding for Selected Infectious Diseases**

| <b>Disease</b>                     | <b>Reported<sup>a</sup> annual cases in the U.S. (year)</b>               | <b>NIH FY 2017 Appropriations<sup>b</sup></b> | <b>CDC FY 2017 Appropriations<sup>b</sup></b> |
|------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Hepatitis C                        | 2,967 (2016) <sup>1</sup>                                                 | \$107 million                                 | \$34 million                                  |
| HIV/AIDS                           | 38,782 (2016) <sup>2</sup>                                                | \$3 billion (9.5% of total NIH budget)        | \$787 million (domestic only)                 |
| Seasonal Influenza <sup>c</sup>    | 9.2-35.6 million <sup>3</sup> (2010-11 to 2016-2017 seasons)              | \$263 million                                 | \$187 million                                 |
| Vector-Borne Diseases <sup>d</sup> | 59,646 (2016) <sup>4</sup>                                                | \$46 million                                  | \$26 million                                  |
| <b>Lyme Disease</b>                | <b>36,429 (2016)<sup>4</sup></b><br>291,430 - 437,150 (2016) <sup>e</sup> | <b>\$28 million</b>                           | <b>\$11 million</b>                           |

Federal funding for each new case of Lyme disease is small relative to other diseases.

- a Reported cases of many diseases and conditions are substantially lower than total estimated cases. This has been documented for hepatitis, influenza, and Lyme disease, among other diseases and conditions.
- b Rounded to the nearest million.
- c CDC estimates for the national burden of seasonal influenza represent a range from low to high over seven seasons.
- d Lyme disease has a separate funding line at CDC for “vector-borne diseases”; reported cases of Lyme disease are excluded from this row.
- e Lyme disease estimates are based on case reporting to CDC multiplied by an 8- to 12-fold factor to account for estimated underreporting.

1 <https://www.cdc.gov/hepatitis/statistics/2014surveillance/commentary.htm>

2 <https://www.cdc.gov/hiv/statistics/overview/index.html>

3 <https://www.cdc.gov/flu/about/disease/burden.htm>

4 <https://www.cdc.gov/mmwr/volumes/67/wr/mm6717e1.htm>



# Background

## Background

Diseases transmitted by ticks are a serious and growing public health concern. At least 20 known infections can result from tick bites. Over the past 25 years, reports of Lyme disease to CDC have increased steadily (see figure 2). Lyme disease is the most common tick-borne disease with an estimated more than 300,000 new cases diagnosed in the United States each year (see figure 3). As tick populations continue to grow and infected ticks expand geographically, the threat to human health intensifies.

Tick-borne diseases can cause severe health complications and are often difficult to diagnose. The current diagnostic approach relies on clinical diagnosis and serologic measurement of antibody responses. However, the limitations of the tests, coupled with scientific uncertainty and gaps in knowledge and education about how to use them, frequently result in misdiagnosed tick-borne diseases. Lyme disease may be complicated by simultaneous infection with other tick-borne pathogens, such as *Babesia* or *Anaplasma*, a condition called coinfection. Moreover, many patients experience chronic and recurring symptoms after antibiotic treatment for Lyme disease, other tick-borne diseases, and coinfections. This chronic illness is poorly understood and often results in significant

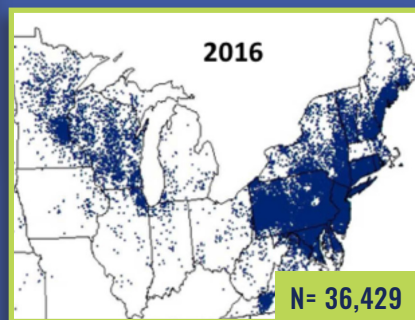
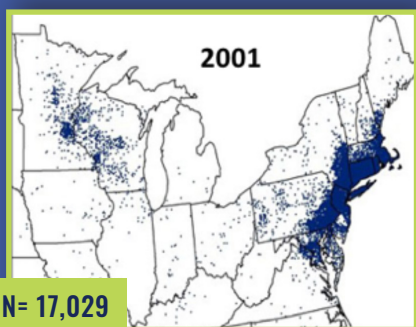
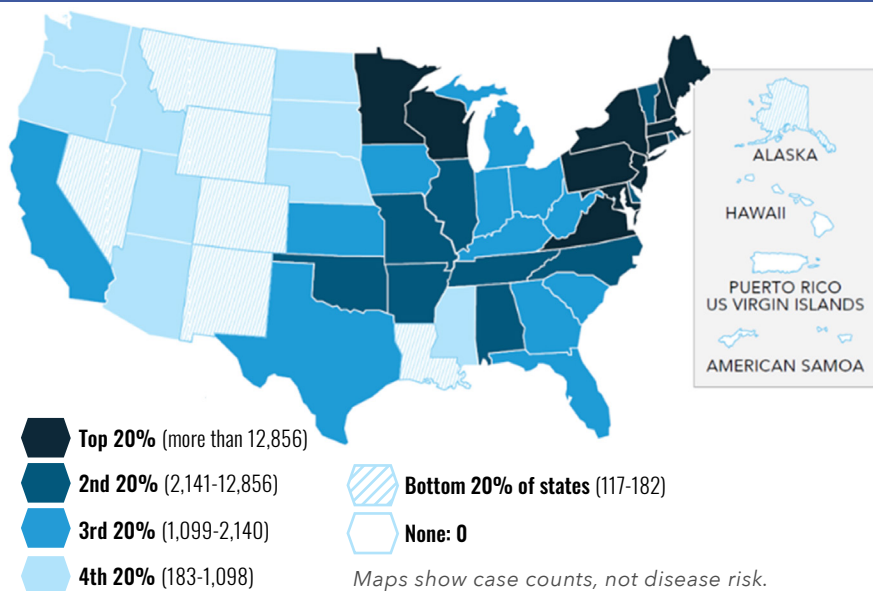
deterioration in the quality of life of patients and their caregivers.

The expense of diagnosis and treatment of tick-borne diseases, paired with loss of productivity, represent a significant economic burden for individual patients, their families, and the American public. The recommendations in this report are intended to address these and many other issues the Working Group identified as having a deleterious effect on tick-borne disease sufferers and public health.

## Congressional Action

In December 2016, Congress passed the *21st Century Cures Act* (see [Appendix E](#)), designed to promote new health care 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. Department of Health and Human Services (HHS) Secretary to establish a Federal advisory committee to review current research efforts and help identify priorities related to tick-borne disease. In response, the HHS Secretary formed the Tick-Borne Disease Working Group (hereafter “Working Group”) to identify gaps in research, education, prevention, and access to care.

**Figure 2: Tick-Borne Diseases in the United States**



Tick-borne diseases affect the entire population in the continental United States. The geographic range of Lyme disease cases has expanded since its first appearance in Lyme, Connecticut, in 1975 and has consistently spread northward, southward, and westward. The high-risk region of the Northeast and Upper Midwest states appears to be converging, over time, in the Ohio River Valley to form one contiguous range. Lyme disease on the West Coast (not shown in the 2001 and 2016 maps) continues to be an important concern, as are risks from other tick-borne diseases.

## Establishment of the Tick-Borne Disease Working Group

The Working Group represents diverse stakeholders, including Federal and public members representing various perspectives and areas of expertise (see Appendix F). The Working Group comprises 14 individuals appointed by the HHS Secretary in December 2017. Seven are public voting members and seven are Federal voting members. Public members include scientists, researchers, physicians, patients and their family members, and patient advocates. Federal appointees to the Working Group represent HHS, the Department of Defense (DoD), and the Office of Management and Budget (OMB)<sup>1</sup>.

A charter approved by the HHS Secretary (see Appendix G) governs the Working Group's structure and activities. 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 Chair and Vice-Chair, appointed by the HHS Secretary, conduct the working group meetings.

<sup>1</sup> The Office of Management and Budget transitioned its Federal voting seat in June 2018 to the HHS Office of the Chief Technology Officer within the Immediate Office of the Secretary, which is more aligned with the mission of this Working Group's charter.



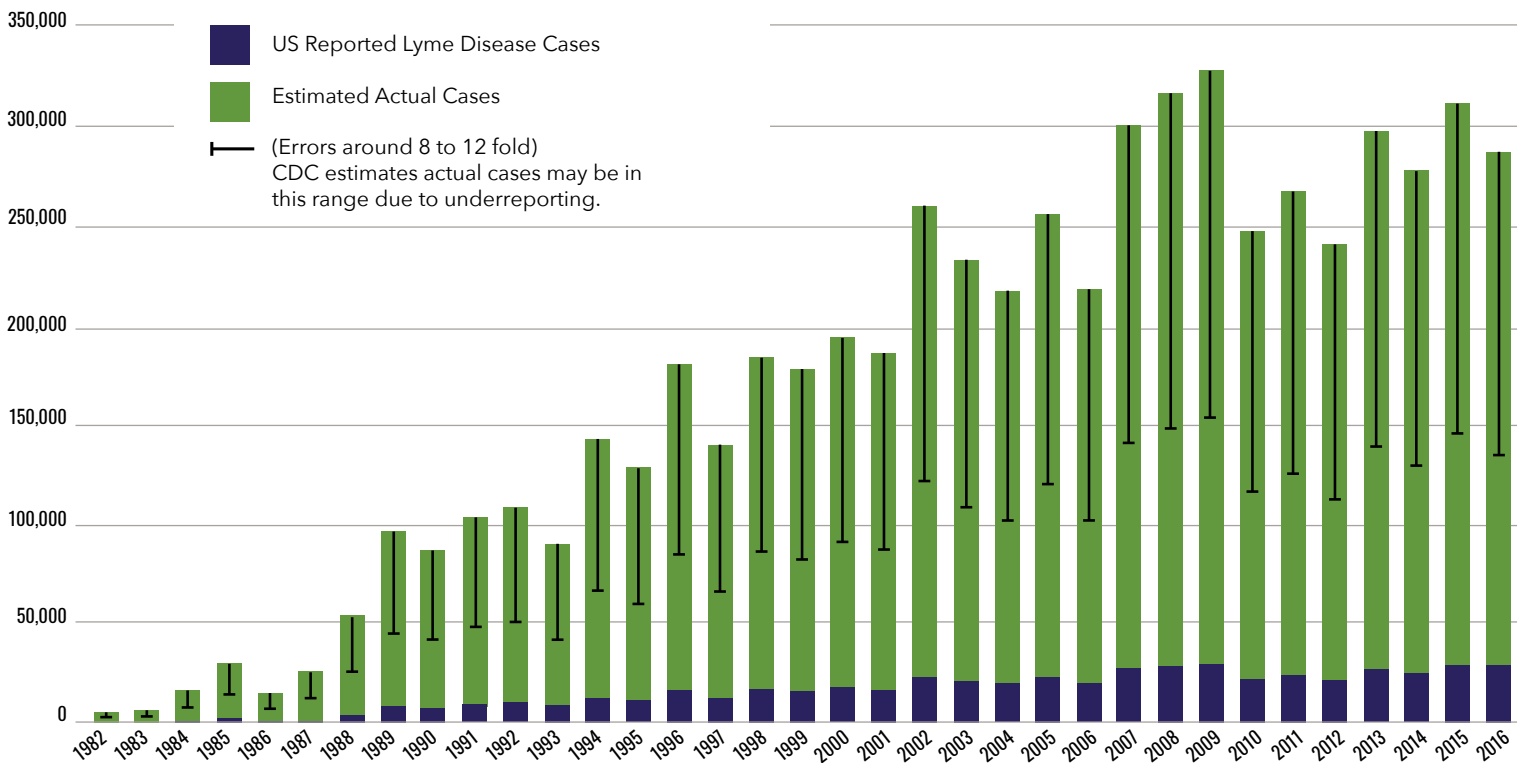
# Report Structure

This report describes a potential path forward for addressing the spread of tick-borne diseases. It is structured according to the priority areas identified by the Working Group, which are:

- Epidemiology and Ecology;
- Prevention;
- Diagnosis;
- Treatment;
- Access to Care and Patient Outcomes; and
- Looking Forward.

Most sections provide a background overview, discuss controversies surrounding the topic, highlight stories from patients about their experiences, and outline research related to tick-borne diseases and current gaps in Federal research and activities. Sections also present recommendations to the U.S. Congress and the HHS Secretary for addressing tick-borne diseases.

**Figure 3: Annual Number of New Lyme Disease Cases**



Across all 50 states and over time, Lyme disease is a growing public health threat with an estimated 300,000 new cases each year, based on case reporting to the CDC multiplied by an 8- to 12-fold factor to account for estimated underreporting. Most Lyme disease patients diagnosed and treated early can fully recover yet an estimated 10% to 20% of the patients suffer from with persistent symptoms that are potentially chronic and disabling. Using a research definition of and data on post-treatment Lyme disease syndrome (PTLDS), the number of PTLDS cases may approach 30,000-60,000 each year in the United States. A precise definition does not yet exist for chronic Lyme disease, so uncertainty is extremely large. The number of U.S. patients with a clinical diagnosis of chronic Lyme disease may be larger, but is unknown.



# Patient Stories

Lyme disease is most often identified at its earliest stage when characteristic skin lesions are frequently present and an accurate early diagnosis is possible. With early diagnosis and appropriate antibiotic treatment, the prognosis of Lyme disease and other tick-borne infections can be excellent. In the majority of patients, early treatment can resolve the acute illness and prevent later manifestations that could occur without timely treatment. In contrast, Ruben Lee Sims' case illustrates what can go wrong when early diagnosis is missed. Such cases do not portray the typical course of most Lyme disease cases but do serve to emphasize the critical importance of accurate diagnosis and early treatment, as well as the complexity of chronic illness that can result from untreated Lyme disease.



## Ruben Lee Sims

Ruben Lee Sims is a Vietnam Veteran who served our country, earned the Vietnam War Campaign Ribbon, and was recognized as the "USAF Comptrollers Top Enlisted Management Analyst of the Year" in 1977. Five years later, multiple tick bites, however, derailed his life. The U.S. Department of Veterans Affairs (VA) was not equipped to diagnose Lyme disease at that time. The military discharged Mr. Sims in 1984, citing "hypochondriasis with psychogenic pain disorder." In 1985, a non-military doctor in San Diego suspected Lyme disease. However, because Mr. Sims had not traveled to New England, the doctor decided that the symptoms could not be caused by Lyme disease. In the words of Mr. Sims, an American hero:

*"I have had Lyme disease while under the direct care of both military and VA healthcare systems. I was misdiagnosed for over three decades and left untreated for Lyme disease. This led to homelessness. Survived attempted suicides. Untreated patients can lose everything, as I did, and become part of the unemployed, under-employed, disabled, and homeless populations that die by suicide and commit violent acts related to the psychological impact of Lyme disease. This is a treatable condition. Please review all emerging science and help prevent Lyme-disease-related deaths and suicides."*

Mr. Sims' psychogenic pain is now confirmed as a symptom of Lyme disease, based on VA's diagnosis. With accurate diagnosis and appropriate treatment, Mr. Sims' physical and mental symptoms have resolved. He shares his story to reach and help other Veterans, especially homeless Veterans, who may be affected by tick-borne diseases.

**Ruben Lee Sims**  
Disabled United States Vietnam  
Veteran  
Lyme Disease Advocate  
Moreno Valley, California



# Methods of the Working Group

## Methods

The Working Group used information from the subcommittee reports, the Federal inventory of activities, public comments, patient testimonies, and the latest available science as a basis for developing this report. This section reviews the subcommittees involved in this work, the Federal inventory, and the public comments received.

## Subcommittees

To leverage member expertise, balance a range of perspectives, and thoroughly examine several aspects of diagnosing, treating, and preventing tick-borne diseases, in February 2018, the Working Group established the following six subcommittees:

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

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

from nine to 13 individuals, not including the leadership team (that is, the Working Group Chair, Vice-Chair, and Designated Federal Officer) that oversaw progress of all six subcommittees. Each subcommittee was led by two Co-Chairs, at least one of whom was a public member or non-government volunteer. Over a three-month period, weekly 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. Before finalizing their reports, subcommittee members voted on the potential actions and included minority opinions expressed by subcommittee members. During



# Methods of the Working Group

Public Meeting 4, 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 transparency requirements of the FACA. Through its work process, each subcommittee drafted a report that synthesized relevant science and identified potential actions for the Working Group to consider. The subcommittees reports were vetted at a public meeting by the Working Group (41 C.F.R. § 102-3.35; 41 C.F.R. at § 102-3.160(a)) and are all available to the public online at: <https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/index.html>.

## Federal Inventory

To gather information on Federal activities that address tick-borne disease, the Working Group developed a Federal project inventory survey, which it distributed to HHS, DoD, and the U.S. Department of Veterans Affairs (VA). As detailed in Appendix D, the Working Group received inventories from CDC, NIH, and DoD. They reported that for fiscal years (FY) 2010 through 2018, the total number of past and current projects is 1,493; and for FY2010 through FY2017, they produced 743 publications.

Of the Working Group's focus areas, CDC and NIH have addressed all but access to care. DoD has addressed disease vectors and surveillance as well as vaccines topics. CDC and NIH have engaged in human surveillance, while CDC, NIH, and DoD have participated in animal surveillance.

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

- Improve early and accurate diagnosis and treatment.
- Strengthen national surveillance.
- Understand the immunological mechanism (for example, the pathogen-host interaction) of immune protection for Lyme disease and other tick-borne diseases.
- Develop new rapid and accurate lab tests.
- Develop antibiotic combination and/or therapeutic options for treating acute and persistent illness.
- Encourage the development of strategic plans for tick-borne disease Federal investments.
- Dedicate funding to tick-borne diseases and evaluate related activities using performance indicators and clear metrics for success.
- Characterize how tick-borne disease affects U.S. national security, military readiness, and the health and wellness of active duty Servicemembers, Veterans, and their families.

## Public Input

In compliance with FACA requirements, the Working Group solicited through multiple channels public comments on issues related to the Working Group's charge.

- **Verbal comments given at Working Group public meetings** - At each of the seven Working Group meetings, time was allocated for the public to provide comment 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](mailto:tickbornedisease@hhs.gov)) at any time, on any day between November 24, 2017, when the email account was established and announced, to July 1, 2018. Emails received before July 1, 2018 were reviewed and addressed in this report. Those received after July 1, 2018 will be considered for the second Working Group report.

There was a general consensus among public commenters that Lyme disease and tick-borne diseases are insufficiently addressed by mainstream medicine and government programs. 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 below by Working Group priority area and for the overall process.

- **Epidemiology and Ecology** - The public would like three or more tick experts, entomologists, ecologists, or vector biologists included in the Working Group

and its subcommittees. They would also like to see funding for comprehensive cost-of-illness studies. They ask that CDC highlight Lyme disease and tick-borne disease distribution across the contiguous 48 states and update the CDC tick distribution map. They also ask that CDC provide weekly, rather than annual, statistics on Lyme disease.

- **Prevention** - The public emphasized that success will stem from awareness and recognition of Lyme disease and other tick-borne diseases. They would like to see renewed prevention efforts but want to avoid another failed vaccine attempt, as there is little trust in the U.S. Food and Drug Administration (FDA) process of fast-tracking vaccines. Prevention efforts should focus on the easiest actions with the highest payoff potential. In short term, the public would like to see more education, behavioral changes, and effective tick repellants. In the medium term, they would like to see tick repellants and tools further improved, continued education and research, and growing trust from acknowledgment of past mistakes. And in the long term, they would like a safe and effective vaccine for humans and/or vectors against ticks. Vaccine safety was a common concern.
- **Diagnosis** - The public would like clarification that "Lyme disease is diagnosed by a combination of medical history, physical exam, and if needed, diagnostic testing." They recommend developing a table that identifies the pros and cons of currently available testing (especially serology) and diagnostics.

They also recommend partnering and/or learning from best practices elsewhere, such as:


- ◇ Technologies applied to other diseases;
  - ◇ Science applied from different disciplines, including fields beyond medicine and those not yet engaged in Lyme disease research; and
  - ◇ Successful programs and potential solutions used by state and local governments and organizations that could be enhanced with Federal collaboration.
- **Treatment** - The public said they need ways to determine if or when Lyme disease infection is resolved. They would like an integrated, interdisciplinary systems-biology approach to understanding Lyme disease, tick-borne diseases, and related immune suppression. They noted the need to revise Western medicine's medical construct of Lyme disease and tick-borne diseases to match the science. They also noted the need to go beyond Lyme disease and include research into combinations of coinfections.
  - **Access to Care and Patient Outcomes** - The public stressed that insurance needs to cover treatment, including long-term antibiotics and immunotherapy, which would be patient-centered and at the treating clinician's discretion. Patients also need to participate in Lyme- and tick-borne diseases-related decisions. They noted that current medical practices are often harmful

and often re-traumatizing patients. The suicide rate is high among Lyme disease and tick-borne disease patients. For this report, they asked that extra care be taken to avoid victim-blaming by ensuring that mental health professionals with tick-borne disease expertise review the language. They also asked that special populations be addressed, such as children, pregnant mothers, Veterans, Servicemembers, migrant workers, farmers, hunters, and outdoor enthusiasts. They would like evidence-based care and policies based on rigorous scientific evidence to be put in place.

- **Process** - The public would like more responsiveness and timeliness from HHS when responding to emails, making announcements, posting meeting minutes, and updating the Working Group's website. They would also appreciate increased transparency. They noted that trust is essential for success, and there is currently little trust in the Federal Government. Many public comments expressed hope that this Working Group will be the "reset" needed to move forward.

## Minority Responses

There were a few recommendations that had opposing viewpoints. These are expressed as minority responses within the relevant chapters.




The Tick-Borne Disease Working Group entails a six-year process, which will evolve and improve over time by incorporating input from diverse stakeholders and emerging science.




# Epidemiology and Ecology


## Recommendation at a Glance: Epidemiology and Ecology

-  **Recommendation 2.1:** Fund studies and activities on tick biology and tick-borne disease ecology, including systematic tick surveillance efforts particularly in regions beyond the Northeast and Upper Midwest.


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-  **Recommendation 2.2:** Fund systematic studies and activities to identify and characterize novel tick-borne disease agents in the United States.


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-  **Recommendation 2.3:** Support economic studies and activities to estimate the total cost of illness associated with tick-borne diseases in the United States, beginning first with Lyme disease and including both financial and societal impacts.

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-  **Recommendation 2.4:** Have public health authorities formally recognize complimentary, validated systematic approaches to tick-borne disease surveillance for humans, such as systematic sampling of tick-borne disease reports for investigation that reduce the burden on tick-borne disease reporting but allow for comparability of surveillance findings across states and over time.

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-  **Recommendation 2.5:** The Lyme disease surveillance criteria are not to be used alone for diagnostic purposes; public health authorities shall annually and when opportune (such as during Tick-Borne Disease Awareness Month) communicate this and inform doctors, insurers, state and local health departments, the press, and the public through official communication channels, including the CDC's Morbidity and Mortality Weekly Report (MMWR).



## Background

In order to understand tick-borne diseases, it is essential to understand ticks, their ecology, and the environment. Despite many scientific unknowns, experts agree that the incidence and distribution of Lyme disease and other tick-borne illnesses are increasing across the United States. This may be due in part to ecological changes in North America since the middle of the 20th century, such as climate and habitat changes, which have set the stage for expansion of tick vectors over large, heavily populated regions.

Beyond conventional biology and ecology methods, tools in microbiology and genetics are essential to understanding tick distribution, disease ecology, and risks to human health. Effective disease characterization and prevention relies on reducing exposure to ticks and disease transmission by identifying and validating effective prevention and control methods and strategies. To track the effectiveness of such measures, it is essential to maintain an accurate understanding of current disease burden and trends against which to measure the success of national prevention strategies and efforts. Controlled field trials that measure both entomologic and epidemiologic outcomes are needed to provide data-driven prevention recommendations.

The CDC currently recognizes 13 unique human tick-borne illnesses in the United States. Seven of those diseases are nationally notifiable (see Appendix D.1). Researchers and health care practitioners continue to discover new disease agents and conditions, which affect increasing numbers of people each year, including novel pathogens like *Borrelia mayonii* and conditions

like alpha-gal syndrome (also known as the “red meat allergy”). Clinical treatment of tick-bite victims is further complicated due to potential for coinfections with pathogens, such as *Anaplasma* and *Babesia*. While not all of these diseases and conditions are nationally notifiable, they are of concern to the public and warrant further attention by the Federal Government due to the increasing frequency and growing threat of tick-borne diseases to public health.

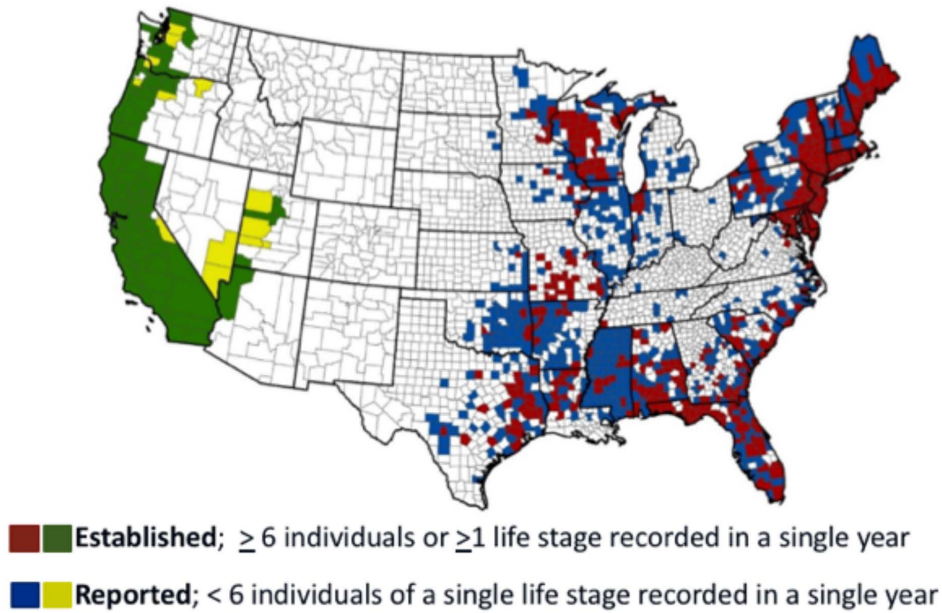
## Major Challenges and Issues

### Surveillance and Burden of Illness

In 2016, Lyme disease was the most common vector-borne disease reported and the sixth most common of all nationally notifiable diseases. While approximately 35,000 cases of Lyme disease are reported each year to the CDC, recent studies indicate that the actual number of annual cases exceeds 300,000 (Hinckley et al., 2014; Nelson et al., 2015). 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. 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.

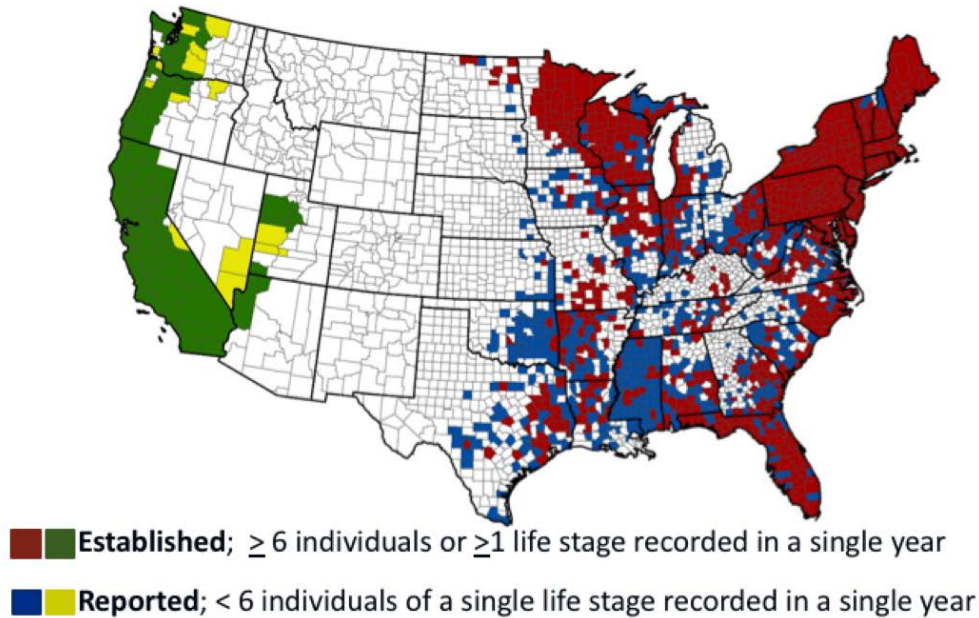


**Figure 4: 1996 - Distributions of Two Tick Species**



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

**2015 - Distributions of Two Tick Species**

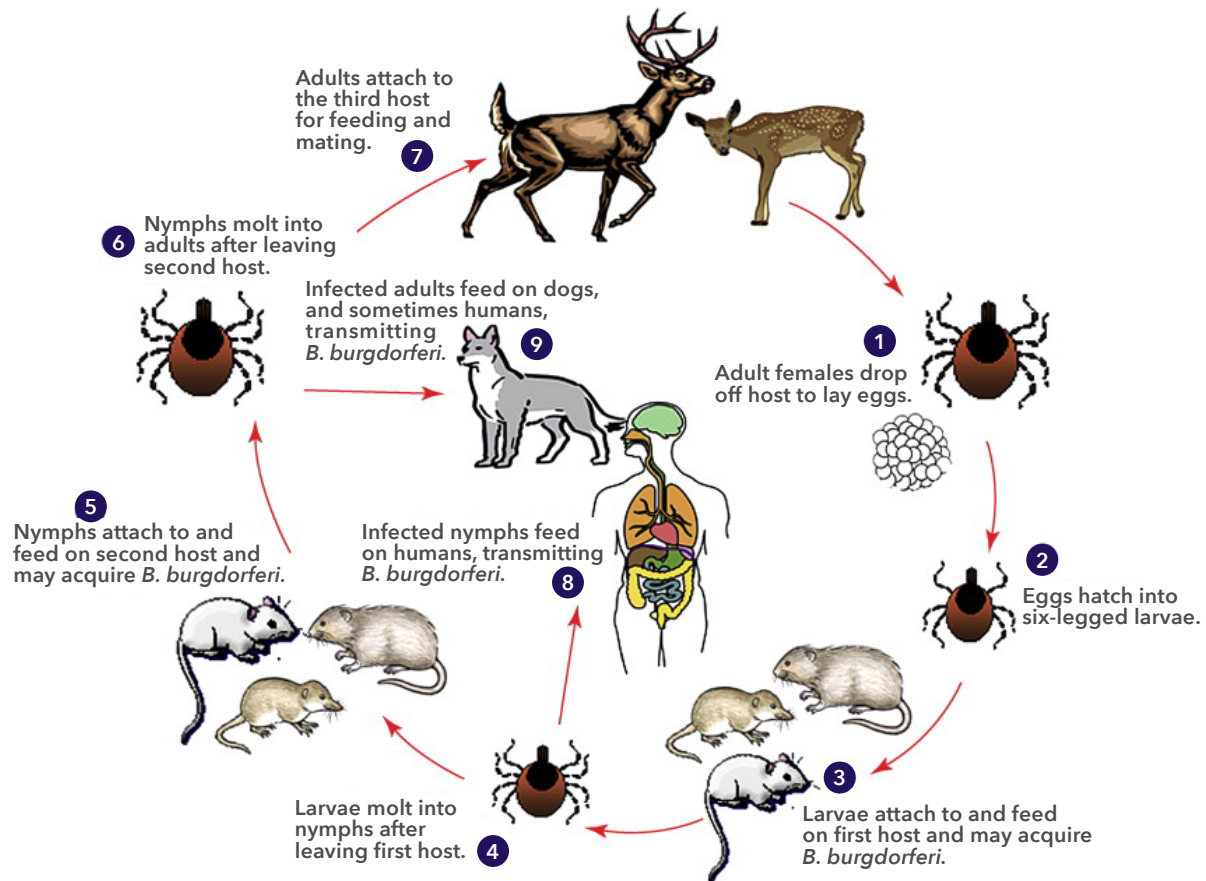


Eisen et al. 2016, *J Med Entomol* 53, 349-386

**Option 1.** The distributions of two tick species, the deer, or black-legged tick (*Ixodes scapularis*) and the western black-legged tick (*Ixodes pacificus*), are shown in U.S. counties between (a) 1907 and 1996 (top image) and between (b) 1907 and 2015 (bottom image). Counties in red or green are "established" for a given tick species, defined as having at least six ticks or two life stages recorded within a single calendar year. Counties in blue or yellow are "reported" for the tick species with one to five reported ticks of a single life stage. Counties shown in white indicate "no records" (Eisen et al. 2016, Dennis et al. 1998). Two previously distinct foci for *Ixodes scapularis* in the Northeast and north-central states appear to be merging in the Ohio River Valley to form a single contiguous focus.



**Figure 5: *Ixodes* Tick Life Cycle and the Transmission of Lyme Disease (*Borrelia burgdorferi*)**



The tick transmission cycle sustains the bacteria, *B. burgdorferi*, that causes Lyme disease. Lyme disease risk is greatest in spring and summer, but can occur during all four seasons. Nymphs, which feed in the late spring and early summer, are responsible for transmitting the majority of infections to humans.

## Disease Vectors

Due to the lack of a coordinated national tick vector surveillance program, there are significant gaps in information on local distribution of tick vectors. This information is a priority and is required to educate the public health community, health care providers, and the general public about local disease risk. Scientists agree that the distribution of tick vectors transmitting human and animal illnesses has increased steadily and significantly in recent decades. The deer, or black-legged, tick (*Ixodes scapularis*) is the vector for Lyme disease, anaplasmosis, babesiosis, tick-borne relapsing fever caused

by *Borrelia miyamotoi*, and Powassan virus disease. The number of U.S. counties where it is established has doubled in the last 20 years (Eisen, Eisen, & Beard, 2016. See Figure 3). Additionally, the number of U.S. counties now considered to be of high incidence for Lyme disease has increased by greater than 300% in the northeastern states and by approximately 250% in the north-central states (Kugeler, Farley, Forrester, & Mead, 2015. See Figure 4). In addition, *Ixodes* ticks have been found in approximately 50% of counties in the U.S., including many counties on the West Coast.

## Recommendations

The working group recommends increased federal investment in the following initiatives, which address the need for a better understanding of vector distribution, disease ecology, vectorial capacity, as well as the need for improved national disease surveillance and reporting with shared standards across all 50 states to define disease burden, patterns, and trends.

### **Recommendation 2.1: Fund studies and activities on tick biology and tick-borne disease ecology, including systematic tick surveillance efforts, particularly in regions beyond the Northeast and Upper Midwest.**

Accurate, current knowledge of the diversity, distribution, relative abundance, and impact of ticks and their associated pathogens is critical for guiding practices aimed at the prevention, diagnosis, and treatment of tick-borne diseases. Unfortunately, the current (2018) understanding of tick transmission risk of various pathogens across states is highly uneven. Standardized approaches at the federal level are needed to achieve the goal of obtaining consistent and reliable data on tick distribution, tick abundance, seasonal activity, and all aspects of tick behavior for the different tick vectors.

To predict where people are at risk for tick-borne pathogens, it is paramount to understand the geographic distributions of vector ticks. There have been very few systematic tick surveys (Diuk-Wasser et al., 2006; Diuk-Wasser et al., 2010; Diuk-Wasser et al., 2012), and thus knowledge of the current distributions of vector ticks is heterogeneous in effort and method. Lack of surveillance data in certain regions, or even localities within regions, gives a potentially false perception of tick-borne disease risk and hinders patients' access to prevention education and timely, accurate diagnosis and care.

When the maps of tick geographic distributions were first published in 1945 (Bishopp & Trembley, 1945), four of the most important tick vectors in the United States were all located in the southern or mid-central regions of the country. However, scientific experts agree that, since then, ticks have been expanding their geographic ranges (Clow et al., 2017; Eisen, Eisen, & Beard, 2016; Hahn, Jarnevich, Moaghan, & Eisen, 2016; Medlock et al., 2013; Sonenshine, 2018). The American dog tick, *Dermacentor variabilis*, now covers almost all of the eastern United States. The blacklegged ticks, *I. scapularis*, has expanded northward into northern New York, all of New England, and parts of southeastern Canada. Similarly, lone star ticks, *Amblyomma americanum*, the major vector of human monocytotropic ehrlichiosis (HME), now covers most of the eastern United



States as well as large areas of the mid-central United States (Monzon, Atkinson, Henn, & Benach, 2016). The Gulf Coast tick, *Amblyomma maculatum*, a vector of *Rickettsia parkeri*, the causative agent of a spotted fever-like illness, has now spread northward along the Atlantic coast as far as Delaware, as well as into the Mid-West to Oklahoma and Kansas, and into parts of southern Arizona. In addition, *Ixodes pacificus* has been discovered in new counties on the West Coast and has been found to harbor the newly recognized human pathogen, *Borrelia miyamotoi* (Nieto et al., 2018).

Risk of tick-borne diseases increases over time due to the complex mix of multiple ecological drivers. Tick range expansion is affected by factors such as climate change, bird migrations, anthropogenic changes in the landscape, increasing populations of suitable host species and suitable tick habitat (Mixson, Lydy, Dasch, & Real, 2006; Ogden et al., 2006; Ogden et al., 2008), reduced populations of predators (Levi, Kilpatrick, Mangel, & Wilmers, 2012; O'Bryan et al., 2018), as well as the introduction of exotic species. Furthermore, the variation in the spatial and temporal risk of acquiring a tick-borne pathogen is impacted by tick-host preferences; host-seeking behaviors; tick vector competency (a tick species' ability to transmit disease-causing pathogens); reservoir hosts (vertebrates capable of hosting tick-pathogens); and the interactions between these diverse factors, which can influence local abundance of infected tick-borne disease vectors.

## **Recommendation 2.2:** Fund systematic studies and activities to identify and characterize novel tick-borne disease agents in the United States.

Safeguarding human health is dependent on early detection, identification, and characterization of novel and emerging pathogens as well as determination of tick transmission risk to humans. Since 2004, seven new tick-borne pathogens have been shown to infect people in the United States (Rosenberg et al., 2018), and these discoveries were made largely in the absence of any coordinated effort. These observations highlight the need for standardized systems and methods using advanced technologies to determine the full scope of disease agents that are potentially transmitted through the bite of an infected tick.

The examination of the tick microbiome is essential for understanding the relationship between microbes and their tick hosts and to facilitate the identification of new tick-borne pathogens. The conventional methods for detecting and identifying causative agents for tick-borne diseases should be supplemented with novel, powerful molecular approaches. These should include metagenomics, which have been shown to be very useful for detecting and identifying pathogens in complex environmental and clinical specimens and has great potential for use in identifying novel tick-borne pathogens.

Understanding which pathogens ticks are capable of transmitting can help address problems associated with the geographic diversity of ticks and the breadth of pathogens they potentially transmit in a specific location of risk. This understanding could also help the Federal Government properly allocate resources to further

investigating unsolved problems, such as the eco-epidemiology of human Lyme disease in the South, and the causative agent of southern tick-associated rash illness (STARI).

**Recommendation 2.3:** Support economic studies and activities to estimate the total cost of illness associated with tick-borne diseases in the United States, beginning first with Lyme disease and including both financial and societal impacts.

To fully understand the impact of tick-borne diseases in the United States, it is important to identify and quantify the significant financial and societal burdens that are associated with them. This may be done with cost-of-illness (COI), or burden-of-disease, studies, which provide an economic analysis to identify and measure the costs of a particular disease to society. Such studies generally include the direct, indirect, and intangible dimensions of the disease. The result or output is often expressed in monetary terms (for example, in U.S. dollars per year) to characterize the total burden of a particular disease to society, communities, families, and individuals. Such methods to assess the financial impact and societal burden can help to inform policy and guide decision makers who must prioritize public health needs, research, and interventions.

Comprehensive COI studies do not exist yet for Lyme disease and other tick-borne diseases. Preliminary studies of direct medical expenses indicate that Lyme disease alone may cost as much as \$1.3 billion per year to treat in the United States. According to Adrion, Aucott, Lemke, and Weiner (2015), individual Lyme disease patients pay an average of \$3,000 in medical costs throughout their course of treatment. These

estimates do not include indirect and nonmedical costs, for example, the costs of traveling to and from doctor appointments, lost wages, loss of employment, and the financial cost to caretakers or services for care. Additional research is needed to fully characterize the drain of tick-borne disease to U.S. society, including medical claims, disability claims, and all of the indirect and intangible costs incurred by tick-borne disease patients and their caregivers.

**Recommendation 2.4:** Have public health authorities formally recognize complimentary, validated systematic approaches to tick-borne disease human surveillance, such as systematic sampling of tick-borne disease reports for investigation that reduce the burden on tick-borne disease reporting but allow for comparability of surveillance findings across states and over time.

Tick-borne disease is an interdisciplinary challenge and national priority that warrants broader data access to facilitate information exchange and more rapidly advance scientific progress. Scientific information and data today are frequently collected and published in white papers or peer-reviewed literature, which provide valuable context for human case data and enhance our understanding of changing tick-borne disease risks. However, they are not yet readily shared or easily applicable across different disciplines. Establishing shared data repositories with requirements to make federally funded science and data open by default and available to the public has the potential to accelerate scientific insights and evidence-based mitigation strategies.

Disease surveillance is a state responsibility, led by the Council of State and Territorial



Epidemiologist (CSTE) in conjunction with the CDC. Traditional public health and disease surveillance is a passive process whereby health care 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 diagnostic laboratory tests. Passive systems are less effective for diseases that are typically diagnosed in outpatient settings and for which there are no definitive laboratory tests (Carter, Lynfield, Feldman, Hook, & Hinckley, 2018), such as Lyme disease.

Lyme disease cases (and to a lesser degree other tick-borne disease cases) are significantly under-reported in the United States largely due to burdensome reporting requirements. Under-reporting and inconsistencies in surveillance data, from state to state and from year to year, significantly hamper efforts to evaluate prevention effectiveness. Additionally, it can result in a lack of awareness on the part of the public and the health care community that tick-borne diseases are a risk in a particular geographic area, leading to failures in diagnosis with potentially fatal consequences.

Pooling diverse interdisciplinary information sources and emerging technologies holds promise for enhancing surveillance, although this approach has not yet been applied to tick-borne diseases. Systematic synthesis of data across nested scales (from local to regional, state, country, and global) is required to understand disease ecology and the implications to human health.

Creative and novel interdisciplinary approaches that are financially sustainable will also be

required to improve public health surveillance of Lyme disease and other tick-borne diseases. One approach that could complement traditional surveillance would be the collection of interdisciplinary datasets across diverse sectors, geospatial data, tick-borne disease reports, companion animal tick-borne disease testing data, crowdsourcing and citizen science data, electronic health records, and insurance claims.

Another alternative surveillance approach could be the use of systematic validated samples. This could include regular sampling of tick-borne disease reports for subsequent public health investigation or laboratory-only reporting. A current example takes place in New York State, where a 20-percent sample of all reports is investigated.

**Recommendation 2.5:** The Lyme disease surveillance criteria are not to be used alone for diagnostic purposes; public health authorities shall annually and when opportune (such as during Tick-Borne Disease Awareness Month) communicate this and inform doctors, insurers, state and local health departments, the press, and the public through official communication channels, including the CDC's Morbidity and Mortality Weekly Report (MMWR).

The Lyme disease surveillance case definition is frequently misunderstood and misused throughout the medical community. According to the CDC, a surveillance case definition "is a set of uniform criteria used to define a disease for public health surveillance... [and is] not intended to be used by health care providers for making a clinical diagnosis or determining how to meet

an individual patient's health needs" (Centers for Disease Control and Prevention (2017)). However, treating practitioners routinely use the Lyme disease case definition to diagnose patients, and insurance companies often require that patients meet the surveillance criteria before agreeing to cover their care. Compounding the issue is the broad misunderstanding in the medical community that patients who do not meet the case definition cannot have Lyme disease. Those patients who have tick-borne disease-related chronic illness yet do not meet the surveillance criteria often face difficulties with obtaining diagnosis, treatment, and medical insurance reimbursement (see chapter 6 on Patient Access to Care and Patient Outcomes).

The Lyme disease case definition requires a "two-tier system" for verification: an Enzyme Linked Immunosorbent Assay (ELISA) test and, if the ELISA is positive or equivocal, a subsequent western blot test. With input from the CDC, the CSTE adopted these criteria in 1994 to verify cases of Lyme disease for surveillance purposes across all 50 states, allowing health officials to compare the number and distribution of cases over space and time (see the minority response in chapter 4 on Diagnosis). The surveillance criteria define areas of the United States as being high or low incidence for Lyme disease.

Complicating the issue, health care providers in low incidence regions, such as the South and the West Coast, are often under the impression that Lyme disease does not occur in their state and therefore do not conduct the two-tier test on patients with symptoms consistent with Lyme disease. As a result, those patients and their family members may need to travel long distances, often paying out-of-pocket, to seek diagnosis and treatment from practitioners in high incidence states (Johnson, Aylward, & Stricker, 2011) (see chapter 6 on Access to Care and Patient Outcomes).

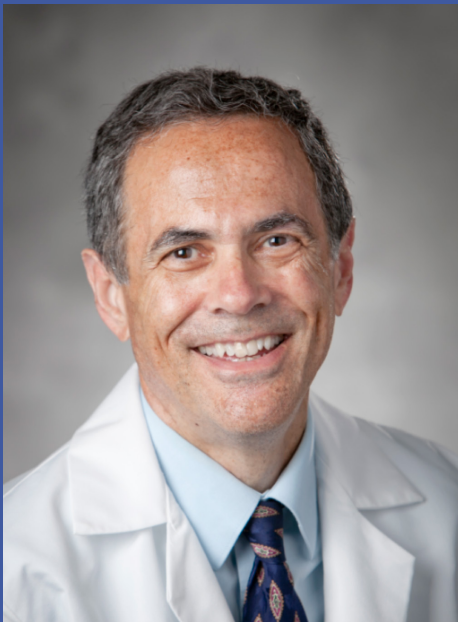
To prevent further patient suffering and societal burden, it is critical that public health authorities clarify and reiterate the message that the Lyme disease surveillance criteria are only intended for disease surveillance and are not to be used alone for diagnostic purposes. The Federal Government is urged to broadcast that message annually, especially during Lyme Disease Awareness Month, using websites, social media, publications, and other outlets. It is recommended that the CDC, in particular, publish this clarification in its Morbidity and Mortality Weekly Report, a respected government publication that is widely read by health care providers.

**Epidemiology and ecology help us understand the magnitude, geographic distribution, and dynamic nature of tick-borne diseases, so we may inform and improve prevention efforts.**





# Patient Stories



## Dr. Neil Spector, M.D.

Lyme Disease Survivor and Patient Advocate

Associate Professor of Medicine  
Duke University School of Medicine  
Durham, North Carolina

## Dr. Neil Spector

Dr. Neil Spector's healthy outdoors lifestyle as a jogger and marathon runner increased his exposure to and risk for tick borne disease. In the late 1980s and early 1990s Dr. Spector lived in New England, which is a region highly endemic area for Lyme disease. Dr. Spector first began to experience a bizarre constellation of symptoms in 1993, which including cardiac arrhythmias and profound fatigue ("I went from running 10 miles a day, six days a week to barely being able to walk 10 yards without feeling exhausted"). Doctors could find nothing wrong with him. In his own words,

*"I was confused. Should I believe a team of doctors assuring me that nothing was wrong? Or follow my gut instinct exhorting me to unearth the mystery responsible for my downwardly spiraling health? I was beginning to question my sanity."*

Dr. Spector's symptoms worsened with time: cardiac rhythm disturbances, migratory muscle pains, weight loss, malaise, insomnia, brain fog, severe fatigue, and more. In 1997, doctors prescribed him antibiotics for an unrelated condition—and, unexpectedly, many of his symptoms including arthritis improved. It was also in 1997 that he was diagnosed with third-degree heart block and ventricular arrhythmias requiring a permanent pacemaker/defibrillator. A diagnosis of Lyme disease was confirmed in late 1997 and despite an aggressive

course of antibiotic therapy, the heart block and ventricular arrhythmias did not resolve. He then progressed to a dilated cardiomyopathy.

Dr. Spector was undiagnosed and misdiagnosed for years. Even as a well-trained, academic physician-scientist with access to the best medical resources in the United States, Dr. Spector's symptoms were dismissing as "stress" related. As a result, Dr. Spector's heart suffered irreversible damage. Lyme carditis—when Lyme disease bacteria enter the tissues of the heart—is considered rare yet serious and potentially fatal. Lyme carditis occurs in approximately 1% of cases based on Lyme disease surveillance criteria reported to CDC, yet more research is needed. This manifestation of Lyme disease brought Dr. Spector to the brink of death. He needed a heart transplant to save his life.





# Prevention

## Recommendation at a Glance: Prevention



**Recommendation 3.1:** Fund additional studies and activities on the development and evaluation of novel and traditional tick-control methods that have shown promise in other areas of public health entomology.



**Recommendation 3.2:** Build trust via a transparent mechanism by which all stakeholders examine and discuss past vaccine activities and potential adverse events to inform future vaccine development in Lyme disease.



**Recommendation 3.3:** Support the development of safe and effective human vaccines to prevent Lyme disease with transparent mechanisms by which all stakeholders examine and discuss past vaccine activities and potential adverse events to inform future vaccine development.



**Recommendation 3.4:** Prioritize education by informing clinicians and the general public about the regional and specific risks related to tick-borne diseases.

## Background

Despite decades of research evaluating tick- and host-targeted interventions, the incidence of tick-borne diseases in the United States continues to rise. Scientists have identified a variety of bacterial, parasitic, and viral disease-causing agents that are transmitted to humans by multiple species of ticks. New tick-borne pathogens continue to be identified, further implicating ticks as an important threat to human health nationwide. Blacklegged ticks, Western blacklegged ticks, lone star ticks, American dog ticks, Rocky Mountain wood ticks, Pacific Coast ticks, soft-bodied ticks, Gulf Coast ticks, and brown dog



### **Figure 6: Enjoying the Outdoors**

Enjoy the outdoors while taking precautions to prevent tick-borne diseases. Know where to expect ticks and how they behave. Ticks live in grassy, brushy, or wooded areas and often wait in leaf litter and at the end of branches and leaves for hosts to brush against them. Stay on the hiking paths and wear proper clothing and use repellants. For more information on avoiding ticks and repellants, visit [https://www.cdc.gov/ticks/avoid/on\\_people.html](https://www.cdc.gov/ticks/avoid/on_people.html) and <https://www.epa.gov/insect-repellents>.

ticks all play important roles as vectors of a variety of agents that cause human disease, with several tick species capable of carrying and transmitting multiple pathogens to humans in a single bite.

A review of the scientific literature and expert presentations has identified the following crucial needs: (1) reducing human exposure to vector ticks, (2) identifying novel methods for controlling ticks and tick-borne pathogens, and (3) conducting further study and adequately validating strategies (including vaccination) aimed at blocking the transmission of tick-borne pathogens to humans and animals.

## **Major Challenges and Issues**

Personal protective measures, such as performing tick checks or wearing tick repellent, are widely recommended for reducing transmission of the pathogens that cause Lyme disease and other tick-borne diseases. Although such measures are simple to perform and inexpensive, they require implementation on a daily basis to be most effective. Also, ticks are tiny and easily missed. Finally, while most people know something about ticks, their current knowledge or well-intentioned

practices are frequently not grounded in evidence or justified by science, so they remain at risk for tick exposure.

Compared with personal protective measures, household and peridomestic (backyard) preventive measures, such as residential pesticide applications or landscape modifications, require more effort and cost up front, but do not rely on daily action for effectiveness. Community-wide interventions, such as deer management, tick management, and educational programming, have the potential for maximum impact on tick populations or disease transmission. However, possible barriers to the implementation of such interventions include municipal and state regulations as well as a significant investment of labor required for sustainable impact.

Effective vaccines against Lyme disease are feasible, as demonstrated by LYMERix, an outer surface protein A- (OspA) based vaccine for human Lyme disease, which was available in the United States between 1998 and 2002. LYMERix had an efficacy rate of nearly 80%. However, it was voluntarily withdrawn from the market because of low public demand. Factors that helped limit uptake of LYMERix included a complicated vaccination schedule, permissive recommendations that required patients and health care professionals to assess risk and environmental exposure, and a theoretical concern that OspA could cross-react with human tissue and evoke persistent arthritis in genetically susceptible vaccine recipients. A major challenge to vaccine development continues to be a concern among some patient groups and practitioners over the lack of transparency in the handling of potential side effects from the LYMERix vaccine (Poland, 2011).

Scientific studies and analyses have found no evidence of elevated rates of arthritis in patients who received LYMERix compared to placebo recipients. Yet public concerns persist with respect to vaccines in general, and Lyme disease vaccines in particular, especially vaccines that are OspA-based. Addressing current barriers to acceptance by the general public and industry will be essential to helping ensure the successful introduction of human vaccines against Lyme disease and other tick-borne infections. Success is likely to require a combination of scientific progress; company, public, and federal agency engagement; and patient advocacy.

## Recommendations

The working group has identified four initiatives that the Federal Government could spearhead to improve the prevention of Lyme disease and other tick-borne diseases.

**Recommendation 3.1: Fund additional studies and activities on the development and evaluation of novel and traditional tick-control methods that have shown promise in other areas of public health entomology.**

### Repellents

In general, skin repellents serve as the first line of protection against tick bites, and several compounds have been identified that effectively repel ticks. However, barriers to using repellents persist and should be evaluated. Also, despite increased public interest in using natural products as tick repellents (Gould et al., 2008a), very few data have been published with respect to the effectiveness of natural products

## Figure 7: Treat your clothing with permethrin



Read instructions



Apply in ventilated area



Hang to dry

specifically marketed for the prevention of human-tick encounters or tick-borne diseases. Furthermore, active ingredients commonly found in natural tick repellents, such as red cedar oil, soybean oil, and peppermint oil, have little or no published data supporting their use for repelling ticks.

Nootkatone, a botanical extract found in grapefruit skin and Alaskan yellow cedar, has shown particular promise for tick bite prevention. It repels blacklegged ticks, a primary Lyme disease vector (Dietrich et al., 2006); is safe and commonly used in food and fragrances; and can be mass produced using a yeast fermentation process. In 2017, CDC entered into a licensing agreement with the biotech company Evolva to further develop nootkatone as an active ingredient in commercially available repellent products, such as repellent soaps and lotions to repel vector mosquitoes. Creating safe formulations of nootkatone has great potential for effective tick bite prevention in the form of soap, lotion, shampoo, or spray for consumer use.

### Protective Clothing

Clothing treated with a pesticide called permethrin has been shown to provide long-lasting protection from blacklegged tick and lone star tick bites (Miller, Rainone, Dyer, González, & Mather, 2011; Vaughn et al., 2014). Multiple studies of military uniforms support the use of permethrin-treated clothing as an effective method of repelling and killing multiple tick species (See Figure 7) (Evans,

To repel and kill ticks, treat boots, clothing, and camping and hiking gear with products containing 0.5% permethrin, which remains protective through several washings.

Korch, & Lawson, 1990; Fryauff, Shoukry, Wassef, Gray, & Schreck, 1998; Schreck, Mount, & Carlson, 1982; Schreck, Snoddy, & Spielman, 1986).

## Rodent-Targeted Transmission-Blocking Vaccines

Some researchers have advocated for tick management strategies involving vaccines that are administered orally to mice via bait containing *Borrelia burgdorferi* OspA. In one study, a rodent-targeted vaccine reduced the incidence of infection among white-footed mouse reservoir hosts and blacklegged ticks in an area where Lyme disease was endemic (Gomes-Solecki, 2014; Richer et al., 2014). In another study, oral vaccination of white-footed mice with bait containing *B. burgdorferi* OspA was shown to prevent infection in mice and reduce spirochete transmission from mice (which had been infected prior to oral immunization) to the ticks feeding on those mice (Voordouw et al., 2013). According to data from a five-year study, a rodent-targeted vaccine resulted in cumulative anti-OspA antibody production and significantly reduced tick infections in the field (Richer et al., 2014). These studies suggest that rodent-targeted vaccines could be effective tools for decreasing the incidence of infection with the Lyme disease spirochete among blacklegged tick nymphs, the primary vector of Lyme disease bacteria to humans. However, it should be noted that the use of rodent-targeted OspA-based vaccines would only prevent Lyme disease, and the use of such vaccines would not reduce tick abundance. Thus, another possible approach would be to use rodent-targeted vaccines containing subolesin, a tick protein. Such vaccines could help reduce tick abundance and disrupt the transmission of

several types of tick-borne pathogens (Bensaci, Bhattacharya, Clark, & Hu, 2012).

The ability of any rodent-targeted intervention to reduce the density of infected nymphs depends on the role of mice or other targeted rodent species in the processes of tick feeding and pathogen transmission. The relative importance of mice may also vary spatially and temporally, depending on their abundance and that of other wildlife hosts. Thus, replicate studies should be conducted to understand how the effects of host-targeted interventions vary in different ecological contexts. Furthermore, any intervention that acts as a selection factor on ticks or pathogens may select for resistance. Thus, research is required to better understand the population biology of ticks and pathogens (for example, migration rates) to help predict the evolution of resistance under different selection scenarios and ecological contexts.

## Novel Genetic Approaches

The development of new genetic and molecular tools is leading to the generation of tick-borne disease prevention tools, including methodologies aimed at creating genetically modified organisms or disrupting gene expression in ticks and reservoir hosts.

The concept of releasing transgenic organisms (for example, animals that have modified genetic material, also known as genetically modified organisms, or GMOs) has long been discussed and tested for controlling populations of vector mosquitoes and crop pests, and may also offer great promise for effective vector control in regions where ticks are hyper-abundant. Transgenic ticks are currently in development



**Figure 8: Create a Tick-Safe Zone Through Landscaping**



- |          |                            |                                                                                                           |
|----------|----------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>1</b> | <b>Tick zone</b>           | Avoid areas with forest and brush where deer, rodents, and ticks are common.                              |
| <b>2</b> | <b>Wood chip barrier</b>   | Use a 3 ft. barrier of wood chips or rock to separate the "tick zone" and rock walls from the lawn.       |
| <b>3</b> | <b>Wood pile</b>           | Keep wood piles on the wood chip barrier, away from the home.                                             |
| <b>4</b> | <b>Tick migration zone</b> | Maintain a 9 ft. barrier of lawn between the wood chips and areas such as patios, gardens, and play sets. |
| <b>5</b> | <b>Tick safe zone</b>      | Enjoy daily living activities such as gardening and outdoor play inside this perimeter.                   |
| <b>6</b> | <b>Gardens</b>             | Plant deer resistant crops. If desired, an 8-ft. fence can keep deer out of the yard.                     |
| <b>7</b> | <b>Play sets</b>           | Keep play sets in the "tick safe zone" in sunny areas where ticks have difficulty surviving.              |

*Based on a diagram by K. Stafford, Connecticut Agricultural Experiment Station*

Make your yard less attractive to ticks and reduce tick populations by clearing tall grasses and brush around the house. Mow the lawn frequently and keep leaves raked. Create a "tick safe zone" with these tips.

at the University of Nevada-Reno, with a goal of using a new genetic tool known as CRISPR to disrupt insulin signaling, which plays a role in nutrient metabolism and, therefore, parasite survival in ticks (Feinberg, 2018). Researchers at the Massachusetts Institute of Technology are also investigating the use of CRISPR technology, which they use to genetically engineer white-footed mice so they are unable to serve as competent hosts for tick-borne pathogens (Harmon, 2016). The use of GMOs may go a long way toward eradicating blacklegged ticks in hyper-abundant areas.

RNA interference (RNAi) is a powerful reverse-genetic approach used to determine gene function and silence tick genes (Fire et al., 1998). Studies of ticks using RNAi technology encompassed the topics of pathogen acquisition and transmission, protective antigens, structural and metabolic proteins, reproduction, digestion, and the roles of salivary gland proteins (Galay et al., 2016). This technology can be used to assess potential targets for pesticides, repellents, anti-tick vaccines, and other strategies to disrupt ticks' physiologic processes and tick-borne pathogen interactions within the tick vector and at the host interface. It can potentially be used to disrupt virus infection within the tick (Hajdusek et al., 2013).

Practical, widescale application technologies and new ways of prolonging the mode of action of RNAi in the tick need to be investigated because this tool could help lead to the discovery of molecules that are essential to tick control and ticks' ability to transmit disease-causing microbes.

**Recommendation 3.2:** Build trust via a transparent mechanism by which all stakeholders examine and discuss past vaccine activities and potential adverse events to inform future vaccine development in Lyme disease.

**Recommendation 3.3:** Support the development of safe and effective human vaccines to prevent Lyme disease with transparent mechanisms by which all stakeholders examine and discuss past vaccine activities and potential adverse events to inform future vaccine development in Lyme disease.

Short of access to clean water, the most effective means for preventing infectious diseases is vaccination. Scientific opportunities abound for human Lyme disease vaccines that would target microbial antigens and/or tick salivary-gland antigens. Avenues that merit exploration include newer approaches to enhance immunogenicity, the removal of components thought by some to harbor autoimmune potential, and protection against multiple species of pathogens.

## Building Trust

For any vaccine to be successful today, diverse stakeholder engagement and trust building are essential. Vaccine activities must be reviewed with a transparent process open to all stakeholders in order to address historical problems and current concerns about potential adverse events. Proactively addressing trust and transparency issues surrounding vaccines—especially surrounding Lyme disease vaccines—will help to



## PREVENTION

inform and improve future vaccine development (Poland, 2011).

### Prospects for New OspA- and OspA/C-Based Vaccines against Lyme Disease

*B. burgdorferi*, the spirochete that causes Lyme disease, produces OspA in unfed ticks. Once the infected tick has been exposed to a blood meal, OspA production is downregulated and production of outer surface protein C (OspC) and other spirochete antigens is upregulated—a process that allows *B. burgdorferi* to be transmitted to, and establish infection in humans. The spirochete demonstrates a remarkably effective corkscrew motility and has other adaptive features that help it to evade host immunity, disseminate, and colonize tissue. Ultimately, that process supports infection, leading to the health problems associated with Lyme disease.

Experts suggest that OspA- and/or OspA/OspC-based vaccines could become available while other types of human Lyme disease vaccines are being developed. For example, a new OspA-based vaccine is in development that was well tolerated and performed well in early trials. It has the advantage of providing protection against strains of *B. burgdorferi* that are common in Europe and the United States, and it lacks the component that was thought by some to be arthritogenic in LYMERix recipients. Another example is VANGUARD crLyme, a subcutaneous OspA/OspC-based vaccine that helps prevent Lyme disease in dogs. Researchers hope that by modifying the approach used to develop VANGUARD crLyme, a similar vaccine may be developed to prevent Lyme disease in humans

and, perhaps, be adapted to prevent additional tick-borne infections as well.

### Anti-Tick Vaccines for Humans: Another Area of Promise

Tick feeding is a slow, multi-stage process that begins with a bite and ends a few days later with full engorgement of the tick. The pathogen that causes Lyme disease resides in the tick's gut prior to a blood meal. After tick feeding has begun, the pathogen migrates to the tick's salivary glands, and the tick injects salivary gland antigens into its host.

Ticks are most vulnerable during the blood meal. For that reason, the ideal anti-tick vaccine would interfere with tick physiology during feeding or prevent feeding altogether. An advantage of such an approach is that it could theoretically prevent transmission of Lyme disease, anaplasmosis, and babesiosis, and potentially other tick-borne infections by interruption of tick feeding. Most pathogens that are transmitted by the *Ixodes* species of tick usually require more than 24 hours of feeding to infect a host. Table 1 summarizes the methods by which vaccines could prevent Lyme disease.



**Table 1: How Vaccines Can Potentially Prevent Lyme Disease**

## Rodent-Targeted Vaccines

- Kill the spirochete in ticks that feed on mice
- Reduce the prevalence of infection among ticks and mice in the treated environment

## Human Vaccines

### OspA-Based Vaccines

- Block transmission of *Borrelia burgdorferi* by killing the spirochete in ticks

### OspA/OspC-Based Vaccines

- Block transmission of *B. burgdorferi* by killing the spirochete in ticks and mammals

### Anti-Tick Vaccines

- Neutralize the tick's attachment proteins that facilitate a blood meal, which impairs tick feeding
- Target the tick's immunomodulatory proteins that affect host immune response, which:
  - ◊ Reduces transmission and/or acquisition of the causative organism
  - ◊ Reduces or partially controls the spirochete load
  - ◊ Impairs tick feeding
- Target allergy or physiology proteins that facilitate tick engorgement or regulate important functions, which impacts pathogen transmission

**Recommendation 3.4:** Prioritize education by informing clinicians and the general public about the regional and specific risks related to tick-borne diseases.

### Education to Increase Awareness of Tick-Borne Disease Risk and Prevention

In the absence of effective strategies for

controlling ticks and blocking the transmission of tick-borne pathogens, we can improve efforts to educate health care professionals and the public about tick-borne disease prevention, and especially about tick biology and best practices for protection from tick bites.

Accurate education on tick-bite prevention is important for all U.S. residents, regardless of where they live, work, travel, or enjoy recreational



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activities. Currently, there is little coordination or consistency in message selection or source, delivery emphasis, or sensitivity to seasonal or spatial dynamics of tick encounter risk. Moreover, few programs use concepts promoting behavioral change in a consistent or effective way.

Also, few of the recommended educational interventions to prevent tick encounters or tick-borne diseases have been thoroughly assessed. Disparities exist in the level of knowledge, perceived personal risk, and use of preventive measures across the human land-use gradient. Thus, targeted tick prevention programs may be best suited for addressing behaviors that increase the risk for exposure. Additionally, studies are needed to determine specific gaps in knowledge and prevention among different segments of the population.

Numerous actions could be taken to improve prevention education at all levels, from individual actions to national interventions. Ample evidence suggests that people who live in areas where Lyme disease is endemic are well aware of the problem and believe that they are familiar with many of the recommended preventive best practices. Based on these studies, initiatives that increase knowledge do not appear to be effective in getting people to consistently engage in behaviors that prevent Lyme disease. Barriers to implementing tick-bite prevention may be related to age, culture, gender, language, perception of risk, and personal experience. Such barriers might be identified through the use of focus group and social marketing surveys conducted with key stakeholder groups (for example, parents, travelers, ESL school nurse educators, and advocacy groups).

However, other segments of the population that live outside of areas where Lyme disease is highly endemic remain at increased risk for exposure

to ticks due to work outdoors, close contact with wildlife (for example, natural resource land managers, ranchers, farmers, and researchers), or travel to areas where the risk for exposure to ticks is unknown (for example, military personnel, wildland firefighters, disaster relief workers, transmission line workers, and landscapers). Although many prevention programs have been developed specifically for Lyme disease, too few programs address the risk of tick bites in general. Much of what has been developed lacks regional relevance for areas of the country where blacklegged ticks are not known to be endemic, yet the risks for many other serious and potentially deadly diseases from other species of tick exist in those regions. The lack of perceived risk has hindered surveillance activities, awareness, and prevention education. That is why the public needs prevention education that is region-specific and addresses travelers' elevated risk for Lyme disease and other tick-borne diseases.

Additionally, public lands that are managed by various state and federal departments and agencies provide opportunities for increased tick exposures to members of the public who use those lands for livestock grazing, woodcutting, hunting, outfitting and guiding, and general outdoor recreational opportunities, such as hiking, fishing, camping, and tourism. Public land managers, visitors to public lands, and military personnel are other stakeholder groups in need of more education on tick-bite prevention to reduce exposure to tick-borne diseases (Johnson et al., 2014). The lack of knowledge about Lyme disease and other tick-borne infections may put unsuspecting visitors at increased risk for disease and decrease their adherence to prevention practices. There is also a significant need for better awareness of ongoing education that takes a regionally relevant approach to prevention.

## Minority Response

This minority response is driven by the Working Group's recommendation to support the development of human vaccines to prevent Lyme disease. This initiative was proposed in the Vaccines and Therapeutics subcommittee report, which includes the statement that human vaccines against Lyme disease should be "a top priority focus." The dissenting minority stresses that all concerns related to the prior vaccine failure need to be understood and addressed before moving ahead to a new vaccine. This process will ensure that the public can make informed health care decisions about the safety and efficacy of any new vaccine.

A multiplex *B. burgdorferi* OspA-based vaccine, fast-tracked by FDA, is now in phase two trials. Yet there are unsettled issues surrounding the failure of LYMERix, an OspA-based vaccine that was withdrawn from the market in 2002. Researchers had indicated that OspA might trigger arthritis, especially in people with an HLA DR4 allele. (HLA genes have different alleles, which are two or more alternative forms of a gene found at the same place on a chromosome [Food and Drug Administration Center for Biologics Evaluation and Research Open Meeting of: The Vaccines and Related Biologics Products Advisory Committee, 1994; Steere, 2006].)

Other concerns relate to possible neurologic complications of the vaccine. One study reported patients who, within several days to two months following receipt of LYMERix, developed either cognitive impairment, including white matter lesions and damage to the myelin sheaths surrounding nerve cells, or cognitive impairment with sensory axonal neuropathy. Later studies focused on additional patients who had reported neurologic adverse events after LYMERix vaccination. These issues were not raised in the Vaccines and Therapeutics Subcommittee report, nor have they been adequately studied or addressed anywhere to our knowledge (Alaedini & Latov, 2005; Latov et al., 2004; Marks, 2011).

At several FDA hearings, individuals testified about becoming crippled after receiving the vaccine. Doctors and some researchers were looking at causal connections. There were reports of the vaccine "causing" Lyme disease, and many thought that the vaccine was retriggering Lyme disease in individuals who had previously been infected. When vaccinated patients reported their symptoms to the physicians who had administered LYMERix, their concerns and other issues were often brushed off as unrelated to the vaccine and were not reported to the Vaccine Adverse Event Reporting System (VAERS) (Smith, 2001). Additionally, VAERS did not include some of the issues raised in physicians' reports. The FDA's own analysis of VAERS data on LYMERix includes mention of nosologists (rather than physicians) taking data, a lack of standardized case definitions, and coding for adverse reactions that depended on the use of certain words or phrases that required cautious interpretation. It also alludes to phase four data, which according to the analysis, will "be important to help evaluate safety concerns." To our knowledge, those data have not been released publicly (Ball, 2001).

According to Smith (2013), "Questions related to the safety and efficacy of the prior vaccine do not appear to have been fully explored nor answered, but have been met publicly instead with blame



being laid at the door of the Lyme disease community for failure of the first vaccine. In this climate, it is not really a surprise that Lyme disease patients and the public are concerned about a new rollout.” The search for a new vaccine should only commence when the science behind the past vaccine failure is understood. That process needs to happen in a transparent meeting of all stakeholders. Meanwhile, vaccines combining both tick-derived and pathogen-derived antigens with the potential to control many different tick-borne diseases might be a good option for public discussion among all stakeholders until consumers are fully aware of the mechanisms of past vaccine failures.

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Prevention strategies include behavioral modifications, repellents, protective clothing, vaccines, and emerging technologies—all important, yet they do not help those already infected with tick-borne disease who need proper diagnosis and treatment today.





# Diagnosis

## Recommendation at a Glance: Diagnosis



**Recommendation 4.1:** Evaluate new technology or approaches for the diagnosis of Lyme disease and other tick-borne diseases.



**Recommendation 4.2:** Include special populations, especially children, in Lyme disease and other tick-borne diseases diagnostic studies.

## Background

Tick-borne infections are an emerging public health epidemic in the United States. The most commonly reported tick-borne infection is Lyme disease. Other tick-borne infections include, but are not limited to, anaplasmosis, ehrlichiosis, babesiosis, rickettsioses, Powassan virus disease, Bourbon virus disease, and *Borrelia miyamotoi* disease. Notably, people can be infected with more than one tick-borne pathogen at a time. Such coinfections often confound diagnosis and treatment.

Despite federal, state, and local efforts to prevent and control the spread of tick-borne infections, the number of cases has continued to increase over the last few decades. This problem

is exacerbated by technical and biological challenges with respect to diagnosis of tick-borne infections, especially Lyme disease. As a result, opportunities for early identification and treatment of tick-borne infections are limited.

In areas where Lyme disease is highly endemic, the infection may be diagnosed without laboratory testing if patients develop a diagnostic skin lesion, known as erythema migrans (EM See Figure 8). However, 20% of patients may not develop this specific rash, and sometimes the rash is not seen or recognized. Additionally, the rash does not always have the stereotyped bull's eye appearance and instead may be uniformly red or reddish-blue without central clearing or the ring within a ring appearance. Laboratory testing to provide evidence of infection with

*B. burgdorferi*, the organism that causes Lyme disease, is recommended for patients who do not show an identifiable EM rash but have symptoms suggestive of Lyme disease. Other tick-borne diseases and coinfections do not necessarily present with a characteristic rash or other agent-specific signs and symptoms (See Figure 9). Therefore, the clinician must rely on testing for evidence of infection with tick-borne pathogens.

## Major Challenges and Issues

Serologic assays that detect antibodies against *B. burgdorferi* are currently the only type of laboratory test cleared by FDA and recommended by CDC for diagnosis of Lyme disease. Published peer-reviewed studies show that serologic tests have technical limitations, such as cross-reactivity between tests for Lyme disease and those for other infectious diseases. Serologic tests also have biological limitations related to how the human immune system reacts to infection with *B. burgdorferi*. Antibodies may not be produced by the immune system early enough or in high enough quantities to meet the detection limit of the test. These limitations make it difficult for health care professionals to determine whether their patient has Lyme disease. Similar limitations are found with tests for other tick-borne diseases and coinfections.

The skin lesion of Lyme disease can take on many appearances and does not always have the stereotyped bull's eye appearance (**panel A**). Most of the time the skin lesion is uniformly red (**panel B**) or reddish blue (**panel C**) and does not have the ring within a ring bull's eye appearance. Multiple skin lesions can occur when the *Borrelia burgdorferi* bacteria spreads through the blood stream to other areas (**panel D**). The rash may not always be seen or recognized especially when in hard to see places or on dark-skinned individuals (**panel E**).

Figure 9: Skin Rashes of Lyme Disease





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Research focusing specifically on the performance of serologic tests for tick-borne disease diagnosis demonstrates that

- Test results can be inconsistent among different laboratories or with different test kits;
- Serologic assays for tick-borne diseases can be negative during the first several days to weeks of infection; (See Figure 10)
- Serology may not detect all cases of tick-borne disease, particularly in persons who do not produce detectable levels of antibodies in response to infection, and in patients who were treated with antibiotics at the beginning of the infection.

Also, many previous evaluations of Lyme disease tests have focused on patients with EM lesions and, as such, the tests may perform less effectively than expected when applied to patients without EM lesions.

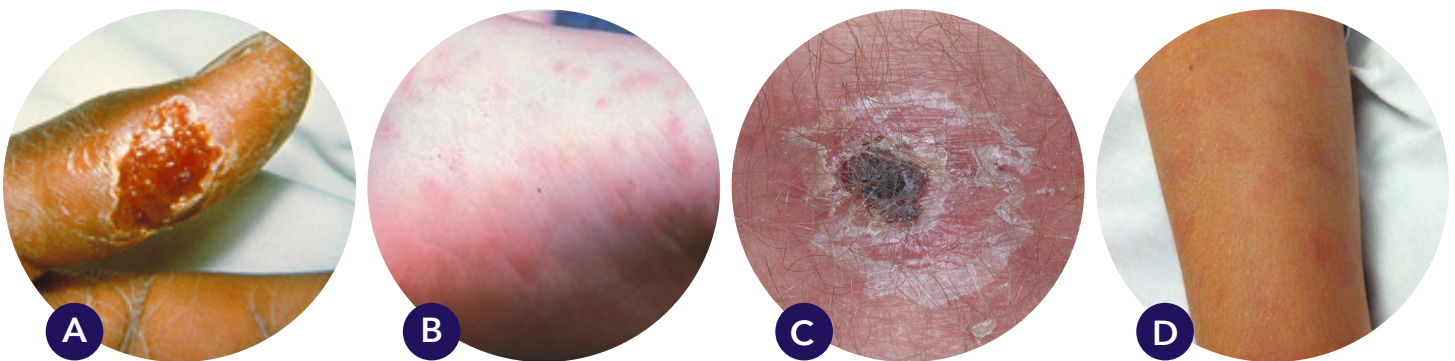
Serologic tests for tick-borne diseases measure a person's past or present immune response to infection and, as such, do not indicate whether

the infection is active. Health care professionals need to know the status of the infection (that is, whether or not it is active) to make an informed decision on whether or not antibiotic treatment should be initiated or continued.

Serology, however, remains the most commonly ordered test for tick-borne diseases in the United States. The greatest threat of not addressing the shortcomings in laboratory testing for tick-borne diseases and coinfections is that a significant proportion of patients in the United States who are newly infected with one or more tick-borne pathogens will not be diagnosed with the appropriate disease, and will not receive prompt or proper treatment for a disease with the potential to cause disabling illness or even death.

The limitations of many currently available diagnostic tests for tick-borne diseases impact their clinical performance and interpretation, which highlights the need for improved approaches to detecting tick-borne diseases and coinfections. The consequences of those limitations include missed and/or incorrect diagnoses, no treatment or inappropriate treatment, increased health care costs, and poorer clinical outcomes.

**Figure 10: Skin Rashes of Tick-Borne Diseases**

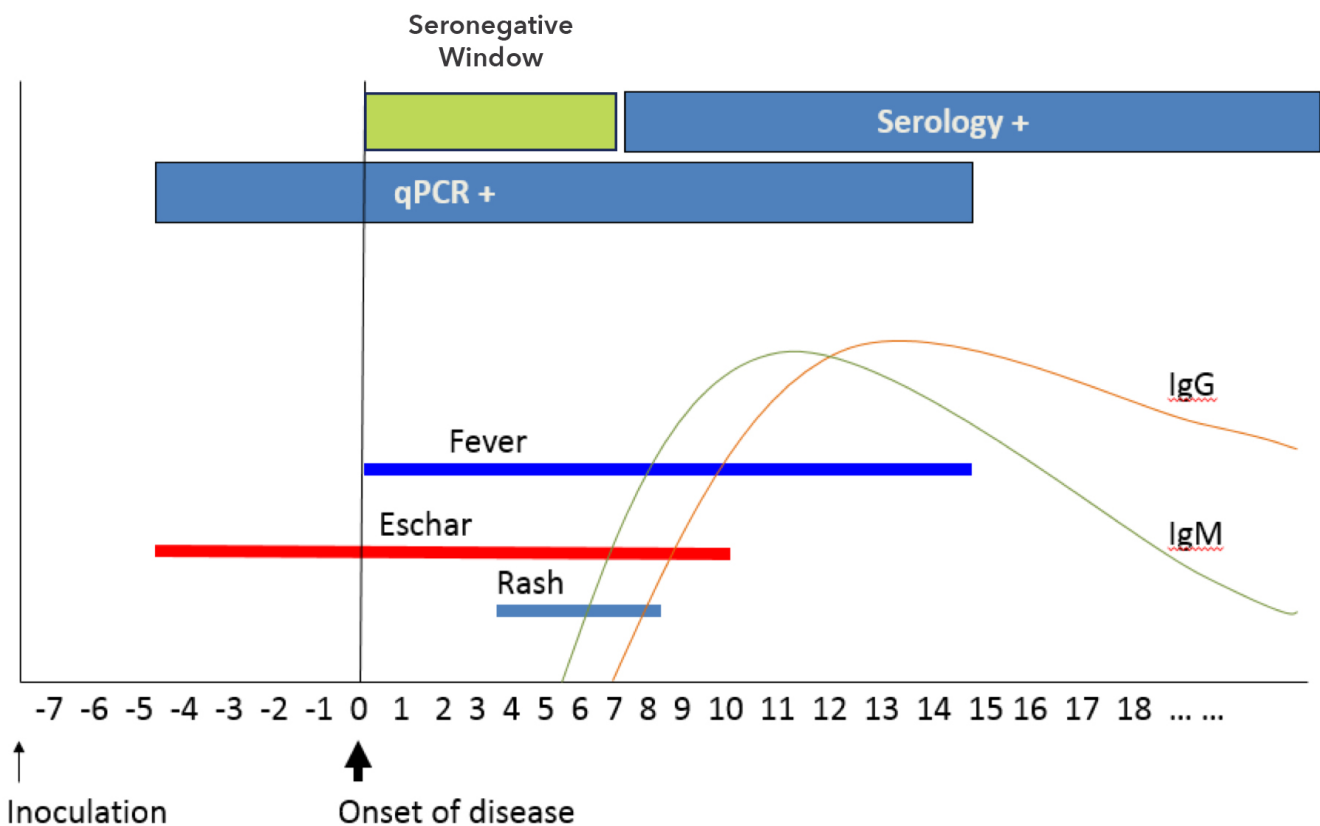


Different tick-borne diseases cause different skin rashes. Tularemia may present with ulcerative lesions (**panel A**). Spotted fever rickettsioses, such as Rocky Mountain spotted fever, may have red spots on the extremities (**panel B**) and *Rickettsia parkeri* with an eschar scab like lesion (**panel C**). *Borrelia mayonii* often presents with round rashes similar to disseminated Lyme disease (**panel D**).



Informed by convergent data from expert presentations, review of peer-reviewed publications, and multiple patient stories shared during public comment, the working group has also identified the need to include special populations (especially children) in the evaluation of new technology or approaches for the diagnosis of Lyme disease, other tick-borne diseases, and coinfections. In endemic areas, Lyme disease cases among children may exceed the number of Lyme disease cases among adults. This statistic highlights the need to include children in scientific studies of Lyme disease and other tick-borne diseases. Equally important is the need to include patients from additional populations, such as pregnant women, as some tick-borne infections pose a risk of maternal-fetal transmission. Populations that were previously under-represented in tick-borne disease studies may hold clues to special risk factors that could help reduce the number of tick-borne disease cases and the resulting burden on the health care system.

**Figure 11: Immune Response in Rickettsial Infection**



During the first weeks of infection, diagnostic tests based on the immune system's antibody response to infection are unreliable. There is a lag time between the onset of symptoms and when tests can measure antibodies, which is called the seronegative window. For example, Lyme disease antibody tests are inaccurate during the first few weeks of infection. Emerging technologies, for example research into PCR tests, hold promise for improved early detection.



## Recommendations

The working group recommends increased federal investment in the following initiatives.

**Recommendation 4.1:** Evaluate new technology or approaches for the diagnosis of Lyme disease and other tick-borne diseases.

### Opportunities for the Development of New Technology or Approaches

The United States is well-positioned to markedly change tick-borne disease diagnosis for the better. A federal response that includes diagnostic test development and implementation would decrease the number of missed diagnoses of Lyme disease and other tick-borne infections, thereby reducing the number of people who have short- and long-term negative health effects due to untreated infections. Additionally, improved tests for tick-borne diseases would reduce the likelihood of false positive and false negative results. Also, current diagnostic measurements do not reliably change with treatment, so there is essentially no “test for cure.” Improved tests for tick-borne infections could decrease the societal burden of Lyme disease and other tick-borne diseases and associated costs to public health care systems. A strong federal response and immediate investment would help enable rapid improvements.

However, recent research has helped us make progress in improving current testing methodologies and also developing new technologies or repurposing existing technologies. Many new tests for infectious diseases have the potential to be diagnostically useful for Lyme disease. Improved serologic tests are being developed that target multiple and more specific components from *Borrelia* or simultaneously detect all tick-borne

infections. Metagenomic sequencing of DNA/ RNA and proteomics can be used to identify tick-borne pathogens in clinical samples.

Transcriptomics and metabolomics are methods of comprehensively assessing a patient’s host response during all stages of infection and can be potentially leveraged for use as a method of staging disease. Emerging technologies and diagnostic platforms—including microfluidics, affinity capture technology, cytokine release assays, and nanopore sequencing—are being repurposed for Lyme disease and other tick-borne infections.

**Recommendation 4.2:** Include special populations, especially children, in Lyme disease and other tick-borne diseases diagnostic studies.

### Opportunities to Include Special Populations in Studies of New Diagnostics

Of the more than 300,000 estimated new cases of Lyme disease occurring each year, more than half occur in children. However, to date, the majority of studies evaluating Lyme disease diagnostics have included few, if any, pediatric patients. Unique challenges in diagnosing Lyme disease in children abound. Those challenges include differences in clinical presentation and a reliance on caregivers to recognize illness and seek care for pediatric patients. Additionally, many health care professionals lack the knowledge that would enable them to suspect possible Lyme disease based on presenting signs and symptoms.

In addition to children, there are other patient populations who have been under-represented in studies evaluating tick-borne disease diagnostics.

Those populations include

- Under-represented minorities;
- Patients from geographic areas with a low reported prevalence of Lyme disease;
- Immunocompromised patients;
- Pregnant women; and
- Neonates born to women who were infected during pregnancy.

Recognition of the classic skin findings in individuals with dark skin pigmentation may be challenging, resulting in delays or even failure to diagnose Lyme disease and other tick-borne diseases. Clinicians who care for patients residing in geographic areas with a low reported prevalence of tick-borne infections require additional education to appropriately suspect Lyme disease, other tick-borne infections, and coinfections in patients with appropriate signs and symptoms *and* to be cognizant of potential false positives and false negatives. Patients with suppressed immune systems may not mount a reliable antibody response to infection; in such cases, reliance on currently available serologic tests may not be appropriate. Moreover, hormonal changes during pregnancy can lead to changes in immune function that may affect the detection of clinical or laboratory findings.

Clinician awareness and recognition of the possibility of Lyme disease and other tick-borne diseases is an important component of the diagnostic process. Most health care professionals have received little or no specific training on the recognition, appropriate evaluation, and interpretation of testing for tick-borne diseases. Clinician and patient education and training should include consideration of additional diagnostic issues pertinent to the above-mentioned special populations.

## Possible Actions

Congress can increase appropriations to NIH and other federal organizations to fund research that will advance the ability of health care professionals to accurately diagnose and effectively treat patients with tick-borne disease. NIH and other federal organizations may then take advantage of current and existing peer-review processes to evaluate the feasibility and impact of proposed research projects, including projects that will

- Support translational research leading to the development of diagnostic tests;
- Rapidly translate new diagnostics into test platforms that can be submitted for clearance or approval; and
- Encourage scientists to repurpose existing technologies available for the diagnosis of other diseases, such as cancer and non-tick-borne infectious diseases.

Other ideas to explore include funding to develop new, or enhance existing, repositories of biological samples for basic research and test validation; private-public partnerships; open source data-sharing; and cash-based prizes for the development and validation of diagnostic technologies.

Additionally, the working group has identified three potential actions that the Federal Government could take to improve testing and diagnosis of Lyme disease and tick-borne infections in children and other special populations. Those actions are to

- Encourage the inclusion of special populations in future federally funded research on Lyme disease, other tick-borne infections, and coinfections;
- Provide federal funds for the development of high-quality tick-borne infection biobanks that include special populations; and
- Develop and disseminate high-quality online clinician education modules that address the diagnosis of tick-borne infections generally, and special populations more specifically.



## Minority Response

This Minority Response was generated to address the working group's recommendation to evaluate new technology or approaches for the diagnosis of Lyme disease and other tick-borne diseases. The recommendation is positive but long range and does not address the immediate problem facing patients who are unable to get diagnosed using the current two-tiered Lyme disease testing system.

The two-tiered system was adopted at the 1994 Dearborn, Michigan, meeting, which was co-sponsored by FDA, NIH, CSTE, the National Committee for Clinical Laboratory Standards (NCCLS), and sponsored by laboratory directors, the state health department, and CDC. It was announced at the meeting that the two-tiered testing system would be part of the surveillance case definition for Lyme disease. A number of experts at the meeting disagreed with the decision because they felt the narrow definition would miss many patients, especially with the unexpected exclusion of some specific bands from the Lyme disease western blot test, bands most likely related to the development of a Lyme disease vaccine.

Health care professionals soon began using the two-tiered surveillance testing criteria in the clinical setting to diagnose patients. Laboratories only reported the CDC-recommended bands of the western blot test, leaving doctors without key information that might have helped them diagnose patients. As a result, more and more patients missed the window of early diagnosis, allowing their conditions to become chronic and challenging to treat, if they were able to get treatment.

A 2005 survey of patients by the California Lyme Disease Association revealed that 73% were denied a diagnosis for Lyme disease at least once due to a negative ELISA test result by CDC criteria, and 31% of those were denied access to a western blot test by their physicians due to a negative ELISA result. The survey also showed that 61% of respondents were denied a diagnosis of Lyme disease at least once due to a negative western blot test result by CDC surveillance band criteria. The survey authors concluded that widespread misuse of the CDC surveillance criteria for diagnostic purposes resulted in significant diagnostic delays and chronic and debilitating illness for patients nationwide (Johnson & Denham, 2005). Band exclusion played a significant role in that scenario. Exacerbating the problem, the Infectious Diseases Society of America (IDSA) incorporated the two-tiered testing criteria into its 2006 Lyme disease treatment guidelines, formally transforming a testing protocol intended for surveillance into a diagnostic protocol for use in the clinical setting, complete with the band exclusions.

If laboratories were required to report out all the bands in the current Lyme disease western blot test, including those that were excluded based on a decision made in 1994, physicians would have access to a valuable tool to help diagnose patients and facilitate treatment, perhaps preventing the development of chronic disease. There is a general agreement that tests using newer technologies need to be developed, and that a meeting should be held involving all relevant stakeholders, including treating physicians, patients, family members, and advocates, to review all interpretive criteria for Lyme disease testing using the newest diagnostic methodologies, techniques, and technologies. Meanwhile, the missing bands need to be restored to the Lyme disease western blot test.

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Emerging technologies and diagnostic approaches, especially those that directly detect active infection, are research priorities. This will give physicians better tools for diagnosis and management of Lyme disease and other tick-borne infections.





# Patient Stories



## David Roth

Retired, Senior Managing Director  
Finance Industry  
New York, NY

## David Roth

In May of 2010, I was a healthy 43-year-old businessman living with my family in New York City. One morning, I awoke with symptoms consistent with a sinus infection that evolved into what felt like the flu. A week later, I visited my internist, who told me I had a viral infection. I mentioned that I had been in areas endemic for Lyme disease, but my doctor did not consider nor test for the illness.

My symptoms worsened in the following weeks. I experienced stomach pain that migrated throughout my body, involuntary twitches in my limbs, joint and tendon pain, difficulty concentrating and memory loss, shortness of breath, difficulty speaking, and insomnia. I revisited my doctor who once again told me it was a virus. This time I requested a Lyme disease test, but the result was negative. As my condition worsened, with new symptoms piling onto the old ones, I saw six more doctors, but none mentioned Lyme disease.

Four months into my illness, I went to a doctor who considered my symptoms and suspected Lyme disease. He ordered a Western blot test (my third), and the result showed all three IgM bands and four of the ten IgG bands. I also sought a second opinion from a "Lyme-literate doctor," who treated me for Lyme disease and later clinically diagnosed me with

babesiosis. With extensive, prolonged treatment for the illness and its myriad symptoms, I slowly recovered to where I am now, about 85 percent of the person I was before I became sick.






During 2010 and 2011, I was tested several more times for Lyme disease. One test came back positive, several equivocal (negative by CDC standards but showing multiple bands), and one indicated I had never been exposed to Lyme disease. I have since learned that the diagnostics used today were developed before most modern technology.

My experience demonstrates that tick-borne diseases are not properly diagnosed and treated in the United States. We need better diagnostics, better treatments, safe and effective vaccines, as well as better medical training and public awareness to combat tick-borne diseases.



# Treatment

## Recommendation at a Glance: Treatment

-  **Recommendation 5.1:** Prioritize research into the potential pathogenic mechanisms (such as immune response, cross-reactivity, autoimmunity, bacterial persistence, coinfections, and other mechanisms) of persistent symptoms in patients who have received standard treatment regimens for tick-borne diseases, including Lyme disease.
-  **Recommendation 5.2:** Promote research on animal models of *Borrelia burgdorferi* infection (that is, Lyme disease) and the mechanisms of disease processes in humans with an emphasis on pathologies that are currently lacking, for example, neuroborreliosis.
-  **Recommendation 5.3:** Improve the education and research on transmission (including transmission via the blood supply and pregnancy) and treatment of other tick-borne diseases and coinfections.
-  **Recommendation 5.4:** Conduct additional clinical trials appropriate to the target populations where gaps may exist.
-  **Recommendation 5.5:** Improve the education and research on the pathogenesis of alpha-gal allergy, also known as the tick-caused “meat allergy.”

## Background

Tick-borne diseases occur in all regions of the United States and are the cause of an increasing burden of disease. Ixodes species alone can transmit multiple human pathogens, including *B. burgdorferi*, the causative agent for Lyme disease. Other tick species such as the lone star tick (*A. americanum*), as well as the American dog, Rocky Mountain wood, and Brown dog ticks (*Dermacentor* and *Rhipicephalus*

species) also transmit serious diseases such as Rocky Mountain spotted fever and ehrlichiosis, which can be fatal if not treated promptly. In addition, coinfections by ticks carrying human and animal pathogens is more widespread than it is commonly recognized by both medical professionals and the general public. The importance of newly recognized agents of disease (for example, *A. phagocytophilum*, *B. miyamotoi*, and Powassan virus) and how they interact with each other in the human host are not yet fully understood (See Figure 11).

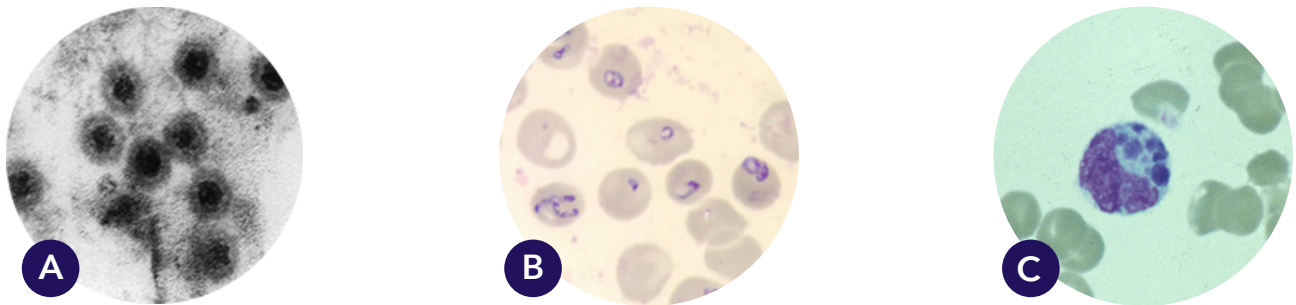
The fundamental goal of most treatment for Lyme disease and other tick-borne diseases is to restore health by treating the disease-causing pathogens. Tick-borne diseases can be bacterial, parasitic, or viral. While bacterial and parasitic diseases are treated by antimicrobials, tick-borne viral diseases, however, are usually treated solely with supportive care. Some tick-borne viral infections, such as the Powassan virus, can lead to permanent neurological symptoms; and no effective treatment exists for severe Powassan virus encephalitis, which has a 10% mortality rate.

While there are many different tick-borne diseases and infections, Lyme disease still accounts for the majority of the known tick-borne disease burden in humans.

The estimate of annually occurring new cases of Lyme disease in the U.S. exceeds 300,000. The costs associated with both antimicrobial and palliative therapies are high. Patients with longstanding untreated disease or with ongoing manifestations may experience short- and long-term disabilities, some approximating the disability experienced with congestive heart failure, and the attendant financial and societal burden can be substantial.

Most individuals who present with symptoms of early Lyme disease, for example erythema migrans lesions (EM) accompanied with flu-like illness, will recover with a sufficient course of antibiotics. However, not all infected humans develop an EM rash, and the EM may not be noticed or correctly identified in some patients. The absence of an EM rash creates difficulties in diagnosis, as “flu-like” symptoms are a non-

**Figure 12: Types of Organisms That Cause Tick-Borne Diseases**



Ticks transmit a range of infections and pathogens, which may be caused by viruses (**panel A**), protozoans (**panel B**), and bacteria (**panel C**). Tick-borne diseases may occur either alone or in combination, which is called a coinfection.



specific finding seen in Lyme disease and associated tick-borne diseases, and might be ignored by patients or clinicians.

Patients may be misdiagnosed early in infection because of insufficiently accurate diagnostics and confusing disease presentations. Unless treated within the first few weeks of infection, patients with Lyme disease may develop a multisystemic illness with clinical inflammatory conditions involving the nervous system, heart, and/or musculoskeletal tissues. Treatment at this later stage of infection can be successful but may result in delayed recovery. Patients may also develop chronic illness, especially those with central nervous system and peripheral nervous system manifestations. Some doctors may choose to treat these patients with additional antibiotics.

The underlying cause(s) of ongoing disease after initial antibiotic therapy has been debated in the medical community and remains a subject of intense discussion. It is imperative to perform further basic research to understand these mechanisms of disease manifestations both before and after treatment, and then use this knowledge to identify and test highly effective therapies to shorten the duration of the illness and minimize the number of people who remain ill following treatment.

## The Immune System and *B. burgdorferi*

A hallmark of the Lyme disease-causing bacterium, *B. burgdorferi*, is its ability to efficiently transmit from feeding *Ixodes* species ticks to vertebrates, disseminate throughout the body, and establish long-term, persistent infection in the absence, and sometimes in spite of, antibiotic treatment. This persistent infection is maintained even when the infected mammal has a complete, functional immune system.

There is strong evidence that *B. burgdorferi* manipulates its host's immune system to enable its persistence. Studying infection in animal models is important because they are the most accurate systems to identify bacterial factors necessary for infection, host mechanisms involved with bacterial clearance or tolerance, and to determine whether a therapy can cure infection. Most of what we know about infection comes from these animal models, including the study of infection in the white-footed mouse (*Peromyscus leucopus*), the natural reservoir species in much of the United States. However, infection manifestations can vary from species to species, and so care must be taken when interpreting these results and their potential applicability to human disease, particularly when comparing immunologic responses in a natural host with that of other mammalian species.

Initially, during a bite from an infected tick, *B. burgdorferi* is passed through the skin into the bloodstream and then throughout the body (See Figure 12). In humans, *B. burgdorferi* disseminates widely via hematogenous, lymphatic, and tissue routes. Common dissemination sites include the musculoskeletal system, skin, nervous system, and heart. Even before *B. burgdorferi* can travel from the tick to the vertebrate, tick salivary proteins are injected through the bite and begin the process of altering the immune system to allow for infection to be established.

*B. burgdorferi* first comes into contact with the innate immune system, including the complement cascade. This cascade is key in the rapid, initial host defense and detects and clears foreign invaders. *B. burgdorferi* infection in mice is known to resist all three pathways of complement cascade activation (classical, lectin, and alternative).



In the second phase of the host response to *B. burgdorferi* infection, adaptive immunity develops. The antibodies of mice are effective in clearing a large number of spirochetes, but not all of the bacteria are eliminated. In mice, *B. burgdorferi* both cloaks itself in host proteins to “hide” from the immune system and rapidly changes the proteins on its outer surface. By performing this antigenic variation, it can outrun the adaptive immune response’s ability to produce specific neutralizing antibodies that match the antigens being produced.

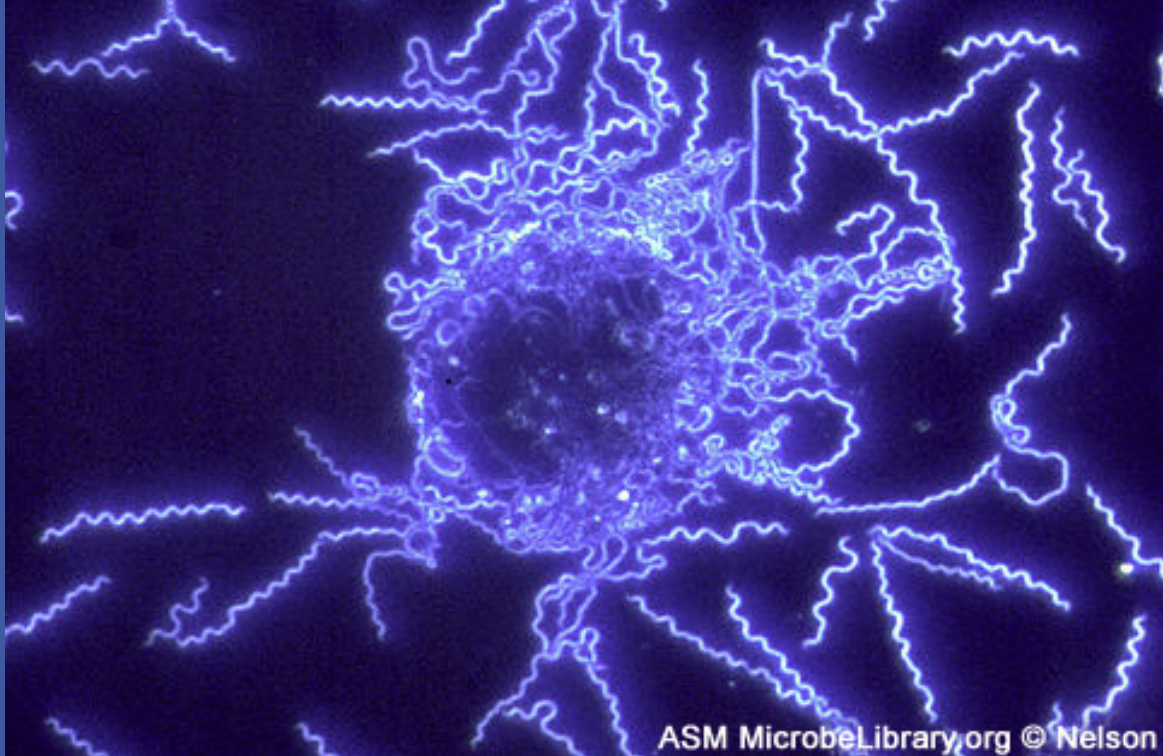
Antibiotic-treated humans who have recovered from infection are susceptible to reinfection. Potential reasons for this reinfection include suboptimal immunologic memory, and/or infection by different strains of *B. burgdorferi*, as demonstrated in several case reports. Recent studies in mice showed a lack of memory B cell and long-lived plasma cell induction following *B. burgdorferi* infection that correlated with a rapid collapse of the lymph nodes usually responsible for immunological memory. This lack of immunologic memory has not been demonstrated in humans.

This reduction in immune response effectiveness was also seen when *B. burgdorferi*-infected mice were vaccinated with another pathogen, in this case influenza, providing evidence for a more generalized alteration of the immune system in mice during *B. burgdorferi* infections. The mechanisms by which this immune alteration is achieved is unknown and merits further study in other mammalian species that are not natural hosts for *B. burgdorferi*.

## Major Challenges and Issues

While most Lyme disease patients who are diagnosed with early acute disease have symptom resolution when treated with appropriate courses of antimicrobial therapy, 10-20% of the patients—based on available data for post-treatment Lyme disease (PTLDS)—continue to experience symptoms that can persist for six months or longer. Patients who remain symptomatic are objectively ill as measured by instruments that have been well validated for measuring symptoms and health-related quality of life. We currently do not fully understand why these patients remain ill following a standard course of antibiotics.

The spectrum of disease manifestations in untreated and PTLDS patients is quite broad. (Note: Patients who meet the research definition of PTLDS constitute a subset of patients who have been diagnosed with chronic Lyme disease). In cases where symptoms and signs of Lyme disease continue following initial treatment, it is difficult to know if they are caused by immune dysfunction, persistent infection by the bacteria or its parts, complications from coinfections, and/or a combination of these and other pathologies. The interaction between tick-borne pathogens, including *B. burgdorferi*, and different components of the mammalian immune system has not been fully investigated, leaving many gaps in our understanding of disease pathogenesis. While studies have shown the ability of *B. burgdorferi* to survive antibiotic therapy *in vitro*, in animals and humans, the pathogenesis of persistent symptoms is not fully understood, and sufficient animal models have



### **Figure 13: *Borrelia burgdorferi* Causes Lyme Disease**

*B. burgdorferi*, the bacterial agent of Lyme disease, is the most common infection transmitted by ticks and accounts for 82% of all U.S. tick-borne disease cases.

not been developed to gain a full understanding of Lyme disease and other tick-borne diseases in humans.

Establishing highly successful treatment regimens for some Lyme disease presentations and other tick-borne diseases is an ongoing challenge for researchers, clinicians, and patients. Current guidelines for recommended treatment may have been in place for a decade or more, with few recent clinical trials being funded despite growing knowledge about diversity and severity of disease manifestations, including fatal cases of Lyme carditis. Although some clinical studies in North America support current antibiotic treatment regimens for Lyme disease, these studies are limited in size and scope, and the endpoints used were not developed in consultation with patients. Treatment trials for other presentations of Lyme disease (for example, neuroborreliosis,

PTLDS, and Lyme carditis) are also insufficient. Recent evaluations by Cochrane (treatment of neurologic Lyme disease) and NICE (Lyme disease treatment guidelines and evidence review in the United Kingdom) found that there is poor evidence based on comparative antibiotic trials to determine the best treatment regimen in Lyme disease manifestations, including early disease and late Lyme neuroborreliosis. The evaluations also noted weaknesses in study design and outcome assessment.

In addition, the discovery of uncommon but potentially important variant strains in humans (that is, *B. mayonii* in the Midwest; other *B. burgdorferi sensu lato* species, *B. miyamotoi*), and regionally variant diversity of *B. burgdorferi* in ticks (especially in the Southeast and the West Coast) have received little research focus to date. Some of these *Borrelia* species may not be



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detected by standard two-tiered testing for Lyme disease and may persist following standard anti-infective therapies and may result in increased morbidity and mortality. New, exotic Asian ticks such as the longhorned tick (*Haemaphysalis longicornis*) have recently been discovered in New Jersey and West Virginia. This tick species has been associated with the severe fever with thrombocytopenia syndrome (SFTS) virus, an emerging hemorrhagic fever discovered in China, as well as the alpha-gal meat allergy in other parts of the world. Resources, therefore, need to be allocated to enhance surveillance, to investigate the pathogenesis, and to determine how to treat diseases associated with these emerging organisms.

Infections caused by bacteria of the genus *Bartonella* complicate tick-borne infections in humans. *Bartonella* species are responsible for some emerging and re-emerging diseases worldwide and can present with illnesses ranging from benign and self-limited diseases to severe and life-threatening illnesses. The primary vector of *Bartonella* is the cat flea, and other known vectors include sandflies, the chiefly European castor bean tick (*Ixodes ricinus*), and body lice. Tick transmission has been confirmed in dogs, and *Bartonella* can be detected in the tick microbiome. While many patients with tick-borne diseases present with symptoms consistent with *Bartonella* infection, laboratory diagnosis can be inaccurate, making confirmation difficult. Irrespective of vector, *Bartonella* infections may play a significant role in tick-borne disease infections, based on case reports and patient registries. Supporting *Bartonella* research is vital to determine the most appropriate therapeutic regimens and to confirm vector competency for North American *Ixodes* tick species.

Lack of scientific understanding of disease mechanisms leads to confusion for both patients and physicians. Patients may not recall having a tick bite-caused EM rash, and may not present with symptoms until months or years after the onset of the infection. Disease manifestations are numerous and span most major body systems, and patients with these diseases can present to many different primary care and specialist clinicians in the outpatient or inpatient settings. In addition, *Ixodes* and *Amblyomma* tick populations have increased, and their ranges have expanded across the country (see chapter 2 on Ecology and Epidemiology). This expansion brings tick-borne diseases and infections to regions where the need for tick-borne disease education programs is not yet fully appreciated nor the curriculum developed.

## Recommendations

The Working Group has identified five initiatives that the Federal Government could invest in to improve the treatment of tick-borne diseases and significantly improve patient outcomes. The first three are interrelated and dependent on one another for success; they are, therefore, presented together as follows.

**Recommendation 5.1: Prioritize research into the pathogenesis (such as, immune response, cross-reactivity, autoimmunity, bacterial persistence, coinfections, and other mechanisms) of persistent symptoms in patients who have received standard treatment regimens for tick-borne diseases, including Lyme disease.**

**Recommendation 5.2:** Promote research on animal models of *Borrelia burgdorferi* infection (that is, Lyme disease) and the mechanisms of disease processes in humans with an emphasis on pathologies that are currently lacking, for example, neuroborreliosis.

**Recommendation 5.3:** Improve the education and research on transmission (including transmission via the blood supply and pregnancy) and treatment of other tick-borne diseases and coinfections.

Our limited knowledge of how tick-borne infections cause human diseases hampers our ability to successfully identify patients and treat them appropriately. The cause of these persistent manifestations in patients may be due to multiple overlapping etiologies increasing an inflammatory process. These could include immune dysregulation, such as autoimmunity or cross-reactivity, bacterial persistence of the spirochete or its parts, or coinfection with additional pathogens such as *Anaplasma*, *Babesia*, and *B. miyamotoi* (relapsing fever). Research on the pathogenic mechanisms of human diseases induced by *B. burgdorferi* and other tick-borne infections, has been sparse and should be prioritized and funded in the future.

One important tool in understanding disease mechanisms in humans are animal models, but each animal model has unique advantages and disadvantages for understanding human disease. Several different animal models have contributed substantially to our knowledge of the bacteria's ability to cause human disease; however, there are many gaps. Studies using these models can contribute to a deeper understanding of disease

processes, including *Borrelia's* ability to evade the immune system and its ability, in laboratory studies, to form "persister" cells that enable its survival despite antibiotic treatment.

In patients with late Lyme neuroborreliosis, neurological manifestation of infection can cause significant morbidity. Patients with neurological disease are more likely to remain ill despite initial antibiotic treatment. While there have been studies on the effects of neurological infection in Lyme disease, there is currently no representative animal model to mimic the disease course of Lyme neuroborreliosis. We similarly lack a full understanding of the role of other tick-borne infections and how they may be contributing to neurological symptoms in those with Lyme disease. Development of a representative animal model to explore the disease course and long-term consequences of neuroborreliosis and other tick-borne infections should be a priority.

Another potential pathogenic mechanism that requires additional study is potential immune suppression by tick-borne pathogens. For example, *Anaplasma* may lead to immune suppression; *Babesia* can worsen clinical manifestations of Lyme disease while leading to impaired clearance of other parasites; and *Bartonella* can act as a stealth pathogen, evading both the cellular and humoral immune response. As shown in recent mouse models, *B. burgdorferi* seem to hamper the production of high-quality, long-lasting antibodies that can control *B. burgdorferi* infection levels, but cannot clear the infection. These studies also suggest that the inhibition of strong adaptive immunity during *B. burgdorferi* infection extends to responses to other pathogens, such as influenza. Whether or not this more general immune suppression occurs



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in humans should be further studied, as it may have diagnostic and treatment implications for patients who are simultaneously or sequentially infected with more than one tick-borne pathogen.

Once a better understanding of underlying causes and mechanisms (that is, disease etiology) in individual patients has been developed, new therapeutic strategies for PTLDS and complex conditions could be initiated. This development should be an area of priority.

It is also important to conduct animal model research on modes of transmission (e.g., maternal fetal transmission, transplant/blood banking) for all tick-borne diseases. *Borrelia miyamotoi* has been shown to be able to survive in human blood components, and other tick-borne infections such as *Babesia*, *Bartonella*, *Anaplasma*, *Ehrlichia*, and *Rickettsia* have been reported to transmit by blood transfusion, and in some cases by organ transplantation. More education about the potential risk of contracting tick-borne diseases after transfusion and/or transplantation is needed so patients can be monitored for tick-borne diseases after these procedures.

Whether persistence exists after an acute infection with the deer tick virus/Powassan virus is an important question, as this has been established for other flaviviruses like Zika and West Nile virus. Presently there is no effective treatment for neurological complications of Powassan virus infection, and serological studies have shown that in Lyme disease-endemic areas, the numbers of individuals exposed are increasing (Knox et al., 2018). Treatment regimens for different infection stages and the impact of delay in diagnosis must be evaluated. It is imperative to support research that studies the effect of simultaneous infection

with multiple tick-borne pathogens in humans in order to improve treatment. Research studies of human tissue—specifically, surgical, biopsy, and post-mortem tissue—are also critical to advancing the scientific understanding regarding the pathophysiology of this infection and how diagnostic and treatment paradigms might be changed to more appropriately treat patients with Lyme disease.

Tick-borne infections are more numerous than previously known, and more complicated clinically than previously recognized. Molecular mechanisms of how these tick-borne pathogens cause disease are poorly understood. Animal models of the different infections are lacking in many cases; when they do exist in some cases, the models are imperfect replications of human disease. Simultaneous or sequential coinfections with more than one tick-borne pathogen may also complicate disease manifestations, diagnosis, and appropriate treatment regimens. More research into the pathogenesis of the different interactions between these pathogens is crucial to improving treatment and patient care and should be a priority for funding.

### **Recommendation 5.4:** Conduct additional clinical trials appropriate to the target populations where gaps may exist.

Establishing highly successful treatment regimens for many tick-borne disease presentations, including but not limited to, Lyme neuroborreliosis, PTLDS, coinfections, and newly recognized tick-borne diseases, is an ongoing challenge for researchers, clinicians, and patients. Recent information has emerged about the breadth of diversity of tick-borne disease clinical

presentations and infections in the United States. Clinical trials for treatment of some aspects of disseminated or late Lyme disease and other tick-borne diseases are limited in size and scope.

While treatment of patients with early Lyme disease can be successful with two or three weeks of antibiotics, clinical trials of more serious manifestations have not established whether this should be the optimum duration of therapy. Guidelines outlining recommended treatment have been in place for a decade or more, but few recent clinical trials have been funded despite growing knowledge about diversity and severity of disease manifestations, including fatal cases of Lyme carditis. In more serious manifestations of the disease, such as Lyme carditis or neuroborreliosis, the evidence for optimal treatment derived from robust clinical trials in North America is also insufficient. This lack of broad-based human trial data hampers our ability to identify optimal treatment strategies for the different stages and manifestations of Lyme disease and tick-borne disease infections in patients.

Recognizing the constraints of traditional research and the opportunities afforded by new technological advances, government institutions are adopting big data, patient-centered research, and personalized medicine initiatives. Examples include patient-powered research networks, patient-powered registries, the National Patient-Centered Clinical Research Network (PCORnet), FDA's Patient-Focused Drug Development program, VA's Million Veteran Program, and the NIH Collaboratory. These 21st-century data tools could hold enormous potential for tick-borne disease research. For example, an existing patient registry has enrolled over 10,000 patients, and data from this registry could identify regimens to

be further evaluated in clinical trials for patients with persistent disease symptoms after treatment.

In addition to trials to evaluate treatments for patients who remain ill after initial treatment, gaps in other patient populations exist.

- **Pediatric population:** Comprehensive studies of children with tick-borne disease—both cross-sectional and prospective—are needed to better understand potential manifestations in the patients who continue to be ill despite antibiotic treatment.
- **Pregnancy:** Transplacental infection of the human fetus has been recognized for relapsing fever borreliosis, as well as Lyme disease, babesiosis, and certain arthropod-borne flaviviruses. Pregnancy poses particular challenges for treatment because few antimicrobials have been approved and are safe to use during pregnancy. Additional research into appropriate treatment options are needed.
- **Other tick-borne pathogens:** The importance of supporting research into treatment outcomes for other tick-borne infections as well as coinfecting patients cannot be understated.
  - ◇ The best treatment regimens for two emerging pathogens, *A. phagocytophilum* and *B. miyamotoi*, are currently unknown and have not been studied in any clinical trials. Presently there is no effective treatment for neurological complications of Powassan virus infection, which can be fatal. In addition, resistance to standard medications for treating babesiosis has been reported in the scientific literature. Newer, more effective



treatment regimens targeting these pathogens are needed.

- ◇ The understanding of the regionality of strains and species continues to evolve. Other *B. burgdorferi sensu lato* species (*B. mayonii*, *B. bissettiae*) are now known to infect humans in North America.
- ◇ There is little understanding if different treatments are necessary when multiple pathogens coexist in the same patients, and if multiple simultaneous coinfections change the accuracy of diagnostics for one or both of these infections. Peer-reviewed literature suggests coinfection of a patient with *Babesia* and *Borrelia* or with *Ehrlichia*, *Anaplasma*, and *Borrelia* result in increased symptoms and a longer duration of illness. Knowledge of how simultaneous coinfections may affect morbidity and mortality is crucial to improving treatment.

To enhance our ability to perform clinical trials more efficiently, a national consortium of investigators and physicians to facilitate Lyme disease clinical trials should be constructed. This consortium should conduct multi-regional trials simultaneously, investigating various agents and treatment durations, using a core set of patient-centered outcomes.

Despite the large number of patients being diagnosed each year, we do not fully understand how best to treat patients with Lyme disease and other tick-borne diseases. 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 health care costs and decrease human suffering.

### **Recommendation 5.5: Improve the education and research on the pathogenesis of alpha-gal allergy, also known as the tick-caused “meat allergy.”**

In addition to infections and diseases, tick bites can also cause other life-threatening allergic reactions such as alpha-gal meat allergy. In the United States, alpha-gal meat allergy occurs in individuals who have experienced prior bites from the lone star tick (*A. americanum*). Unlike other tick-borne diseases, this illness is not thought to be caused by an infection, but by the development of the antibody immunoglobulin (Ig) E against the carbohydrate oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), which has been found in the gastrointestinal tract of at least one species of ticks. In patients with convincing evidence of IgE-mediated alpha-gal allergy, the allergic reaction can begin within several minutes or can be delayed three to six hours after ingestion of meat. It can present with rash-like (urticarial), gastrointestinal symptoms, and airway obstruction (angioedema). Fatalities are rarely seen, but it can be life-threatening with anaphylaxis. Patients react to a carbohydrate antigen in all non-primate mammalian meats, gelatin (highly sensitive individuals may react to bovine serum albumin (BSA) in a drink or gelatin in a capsule), or very rarely, dairy. Personal care products, certain medical products, and nutritional supplements are not typically implicated in alpha-gal meat allergy, although anecdotal cases have been discussed.

The magnitude of the problem and the true number of cases of alpha-gal allergy is unknown. There is very little awareness of alpha-gal allergy and it is not a reportable disease. Endemic regions in the United States correspond with the



distribution of lone star ticks, which range from Long Island to the Southeastern states, although its range has expanded rapidly and extensively across much of the eastern and Midwestern United States during the last 50 years. Some authorities have suggested that the number of cases of alpha-gal meat allergy may be as high as the number of other tick-borne infections. The number of cases is likely to increase as the geographic range of lone star ticks expands.

Increased awareness and public health education programs targeting both the general public and clinicians in endemic areas are, therefore, needed. In addition, raising pre-diagnosis awareness and providing counseling and education after diagnosis on how to prevent exposure to the allergen will help to improve the care of those suffering with this potentially life-threatening illness.

## Education: Signs, Symptoms, and Treatment

There is an urgent need to educate health care providers on the signs, symptoms, and treatment of these tick-borne infections and tick-caused allergic reactions. Recent published reports of several deaths caused by undiagnosed cases of Lyme carditis and Rocky Mountain spotted fever, as well as the rising cases of alpha-gal allergy, illustrate the vital importance of comprehensive medical education for all tick-borne diseases, as well as tick-caused allergies and conditions.

Manifestations of tick-borne infections are numerous and span most major body systems. Because of the diverse and migrating clinical symptomology, patients with tick-borne disease

can present to many different primary care and specialist clinicians in the outpatient or inpatient setting, for example, internal/family medicine, pediatrics, emergency medicine, cardiology, rheumatology, neurology, and psychiatry. According to patient testimonies given to the Working Group, multisystemic manifestations of tick-borne disorders combined with inaccurate diagnostics and lack of effective treatment protocols resulted in misdiagnoses, increased suffering and disability, as well as increased out-of-pocket health care expenses. On the other hand, there is substantial concern in some of the medical community that misdiagnosis due to inaccurate diagnostic tests for tick borne disease may lead to unnecessary therapies, especially when symptoms persist after standard treatment. A comprehensive review of all current, real world evidence, including basic research evidence and clinical evidence from tick borne disease specialists, for diagnosis and treatment of tick-borne disease for clinicians and the general public should, therefore, be undertaken. Additional comprehensive clinician education should highlight diverse symptomology, expanding geography of infecting ticks, and limitations of current testing and treatment protocols. The content must be developed with input from research scientists, physicians, and patients to provide broad but rigorous content to medical providers and the general public.



### Minority Response

While submitted as a Minority Response, the author believes that the essence of this content reflects a point of view shared by a broad community of clinicians and researchers. All authors of the Treatment chapter agree on the general recommendations presented in this chapter. We also agree on the importance of enhanced research into the pathogenesis of PTLDS and other situations associated with persistent symptoms after antibiotic treatment, as well as the need for increased support for research into different aspects of the treatment of Lyme disease and of tick-borne diseases in general. However, as a fusion of work of several subcommittees, the chapter posed challenges for the authors to integrate differences in emphasis and priority, as well as the interpretation of the existing science. The following comments regarding gaps and priorities differ in some respects from those presented in the Treatment chapter.

### Additional Research Gaps in the Treatment of Lyme Disease

At least nine randomized clinical trials of antibiotic treatment of early Lyme disease have been conducted in North America, and several additional studies have been conducted in Europe. While heterogeneous in the choice of antibiotics compared and in study design, these studies are consistent in 1) their demonstration of the effectiveness of standard treatment strategies, and 2) treatment recommendations. In addition to the clinical studies mentioned above, a large retrospective two-year study reviewed the outcomes of standard antibiotic regimens in more than 600 patients with early Lyme disease. Results of the study demonstrated that subsequent reinfection (4% of the cases) was more common than treatment failure, which underscores the importance of ongoing preventive measures for those at risk (Kowalski, 2010).

This is not to imply that additional research cannot lead to improvements in these treatment strategies for early Lyme disease, but rather that research priorities may be best focused on the refinement of available treatment options for the most problematic, yet less completely studied, manifestations of Lyme disease, such as neurologic complications of Lyme disease or persistent Lyme arthritis. In addition to comprehensive clinical measurements, future treatment trials, ideally, should also assess candidate biomarkers to gain insights into pathogenesis and to evaluate post-treatment effects.

## Research Gaps in Treatment of Other Tick-Borne Infections

While at least five different antibiotic agents of several classes are effective in the treatment of Lyme disease, currently only one available antibiotic class has been proven to be effective for several serious tick-borne diseases (that is, *anaplasmosis*, *ehrlichiosis*, and *rickettsial* diseases), and that antibiotic class carries a contraindication to its use during pregnancy. In regions of the United States where Lyme disease is infrequently transmitted, ehrlichiosis and/or other *rickettsial* infections may cause the greatest burden of tick-borne disease. *Babesiosis*, transmitted by black-legged ticks and through blood transfusion, is on the rise in a wider geographic area and can cause an acutely life-threatening infection in persons with immune compromise. Currently available treatment options are usually effective, but limited. All of these tick-borne diseases cause human illness primarily as sole infections, though coinfections can occur with more than one pathogen, if the pathogens are transmissible by the same tick species.

In determination of the priority of research focus, it is important to discern the regional differences in diseases transmitted and their impact. Scientific and clinical precision is required given the diversity of tick-borne microbial pathogens and the overlap in some of their clinical presentations.

**The lack of understanding and agreement on the cause and treatment of patients with chronic symptoms after treatment of tick-borne diseases has left patients in a divided world of controversy without adequate access to affordable care.**





# Patient Stories



## Colonel Nicole Malachowski (USAF, Ret.)

Career officer, leader, fighter pilot  
First woman pilot, USAF Air Demonstration Squadron ("Thunderbirds")  
Springfield, VA

## Nicole Malachowski

My name is Nicole Malachowski. I am a mother, wife, and retired U.S. Air Force colonel and F-15 fighter pilot; and I have neurological tick-borne disease.

In the summer of 2012, while still serving in the Air Force, I went to see a doctor about a growing rash on my right hip and was given 10 days of doxycycline and a topical cream. However, my condition worsened despite the treatment. Within a month, I began experiencing fevers, malaise, and burning sensations. A few months later, I began experiencing neurological symptoms. One day while leading a formation of F-15E fighter aircraft back from a training mission, I was overcome by an overwhelming sense that my aircraft was turning left, thought it was not; and I could not get my hands to activate the switch that I had activated thousands of times. After I finally managed to activate the switch, I realized that I could not speak. Fortunately, my experienced wingman led us home, and the instructor Pilot in my jet performed backseat landing.

However, that day marked the beginning of my medical odyssey. In the following four years, I saw more than twenty doctors across eight specialties. My neurological symptoms continued to worsen, but none of the doctors knew why and some suggested it was all in my head. I was suffering from intensifying fatigue, joint and muscle pain, vestibular issues, ocular manifestations, sensory problems, cognitive dysfunction, and the list goes on. I was misdiagnosed with everything from possible multiple sclerosis, to autoimmune disease, to fibromyalgia. Eventually I could no longer work in the military as a fighter pilot, and the military began steps to medically retire me—I

was permanently, medically retired from the career I loved at the age of 43, after having served in the military for more than 21 years.

By August 2016, my condition had deteriorated so much that I was having extreme difficulty with speech and memory, and I could barely walk. Determined to find out the cause of my medical issues, my husband and I poured through my medical records and all signs pointed to the rash from 2012 and a tick bite I got in the following year while I was stationed in Rhode Island.

Out of sheer desperation, I reached out to a group of doctors specializing in tick-borne disease in Boston. They ordered tests that confirmed neuroborreliosis (*Borrelia hermsii*), neurobartonellosis, babesiosis, and anaplasmosis, confirming severe neurological tick-borne disease. The doctors immediately started treating me with IV antibiotics. Within 10 days, my daily fevers, chills, sweats, and sleep disturbances were gone. Within a few weeks, my ability to find words improved and I could communicate again. However, I was not able to speak fluently for several more months.

Because my illness went undiagnosed for so long, it is challenging to say how long I will need treatment and how long my recovery will last. But I can tell you this: I went from someone who literally could not get out of bed to someone who can take her seven-year-old twins to their soccer games. While I have not recovered completely, I now have a life worth living. I would never have gotten to this point without the accurate diagnosis made by competent, experienced physicians who knew how to recognize and treat the devastating tick-borne illness that so many other doctors missed.



# Access to Care, Patient Outcomes

## Recommendation at a Glance: Access to Care, Patient Outcomes

- 🎯 **Recommendation 6.1:** Create a federal repository for information on Lyme disease and other tick-borne diseases.

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- 🎯 **Recommendation 6.2:** Allocate increased funding for tick-borne disease in the areas of research, treatment, and prevention proportional to the burden of illness and need.

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- 🎯 **Recommendation 6.3:** Ensure the rights of those dealing with Lyme disease and tick-borne diseases and conditions by reducing the burden of the processes under which patients are currently diagnosed and treated and by which they access care. Basic protections must include, but not necessarily be limited to, those that:
  - 🎯 **Recommendation 6.3(a):** Protect patients from employment discrimination.
  - 🎯 **Recommendation 6.3(b):** Protect students of all ages from discrimination.
  - 🎯 **Recommendation 6.3(c):** Protect patients from health care and disability insurance coverage and reimbursement policies that are unduly burdensome.
  - 🎯 **Recommendation 6.3(d):** Protect the rights of licensed and qualified clinicians to use individual clinical judgment, as well as recognized guidelines, to diagnose and treat patients in accordance with the needs and goals of each individual patient.

### Major Issue 6.4—Testing and Diagnostic Bands:

How They Are Used Today and What That Is Doing to Patients

- 🎯
  - Empower patients with data
  - Engage diverse stakeholders
  - Relay information as a neutral knowledge broker Background



## Background

The majority of people diagnosed with early, acute Lyme disease or other tick-borne disease are properly treated and make a full recovery; yet many others are not so fortunate. This chapter focuses on the patients in the latter category and the challenges they face in the United States today. Their numbers and the full scale of the problem are unknown.



### Figure 14: Health Insurance Claims

Health insurance claim denials and the resulting financial challenges are obstacles for patients seeking treatment for tick-borne diseases, especially for complex cases.

In a 2009-2010 survey of nearly 2,500 chronic Lyme disease patients in the United States with positive laboratory testing and chronic symptoms, 49.5% of respondents reported traveling 51 miles or more to see a treating doctor (Johnson, Aylward, & Stricker, 2011). Half of the respondents reported seeing at least seven physicians before the diagnosis of chronic Lyme disease was made. And most respondents experienced symptoms lasting six months or more despite receiving at least 21 days of antibiotic treatment. The follow-up survey in 2013 indicated that chronic Lyme disease patients made an average of 19.4 doctor visits per year, compared to the general population, which makes on average 3.7 visits (Johnson, Wilcox, Mankoff, & Stricker, 2014). As evidenced by the survey results, those who currently have chronic tick-borne disease in the United States are unlikely to receive a proper diagnosis from the first provider they see.

Patients and caregivers who are new to tick-borne diseases and unfamiliar with the past and present science and politics surrounding them are often surprised to discover that the path to diagnosis, treatment, and long-term support for their illness is fraught with obstacles and misinformation. Nevertheless, they must navigate the road to wellness despite high personal and out-of-pocket costs as they strive for a return to optimal health.

The recommendations in this chapter are geared toward finding creative ways to help tick-borne disease patients and their loved ones overcome the significant and often unnecessary burdens they must endure by eliminating recognized barriers to affordable, appropriate, and patient-centered diagnosis, treatment, and care. In co-creating these solutions, a diversity of voices and

opinions must be heard, valued, and considered along with the scientific evidence. Patient and caregiver voices are, after all, data and should be included in the scientific process. Moreover, the individual patients and their needs and experiences must be at the center of this effort to prevent further suffering and ensure the health of the nation.

## Major Challenges and Issues

As they struggle to access care, tick-borne disease patients and their caregivers experience myriad stressors, including the loss of the role they play in their communities, at school, at work, and within their families. Many withdraw from social activities, abandon career or school plans, eliminate hobbies, and place other relationships on hold to become caregivers, advocates, case managers, negotiators, researchers, transporters, record keepers, emotional supporters, and errand-doers. Finances become strained as family members and patients consider selling or taking out loans against their homes, reducing the family to one car, giving up their jobs or interrupting their careers, and abandoning planning of all kinds so that they can tend to the unpredictable day-to-day needs and condition of the patient.

Tick-borne disease patients and their caregivers also report significant strain on their relationships. Spouses become caregivers. Divorces occur, with children and their treatment protocols sometimes used as collateral in divorce and custody proceedings. Healthy siblings feel marginalized and risk developing behavioral issues. Friends retreat. And isolation, which is already a substantial public health issue, becomes



**Figure 15: Extensive Medical Records**

One patient's set of medical records from dozens of doctors and medical visits for tick-borne disease.

a significant contributing factor that adversely affects the overall quality of life and well-being of the individual, the family, and the entire support network.

The health impact on caregivers is also well documented. Research demonstrates higher levels of depression as well as immune system compromise years after the care giving has ceased (Vitaliano, Young, & Zhang, 2004). This contributes to the onset of chronic illness and the resulting costs. Other challenges include job loss, inability to prepare for retirement, and depletion of educational accounts. Providing support to caregivers is imperative, not only to relieve



### **Figure 16: Patient-Provider Relationship**

Knowledgeable and compassionate health care providers are important to treatment success in patients with chronic conditions related to tick-borne disease. These patient-practitioner relationships often involved shared decision-making to evaluate treatment options, potential risks, and potential benefits depending on the unique situation.

their suffering, but also to reduce the full cost to society as a whole.

Patients report significant and repeated experiences with medical staff who are disrespectful and confrontational. Patients talk about the stress of needing to obtain medical care from providers who do not believe them, do not see their suffering as real, and who hold all of the power in terms of access to medical care. This can result in symptoms of medical trauma, including avoidance, anxiety, intrusive memories, intense emotions or numbing, and hyper-vigilance, and impact the patients' sense of safety and optimism for treatment. Children are more vulnerable to the impact of disbelief; and parents report stress and anxiety as they

struggle to maintain employment and parent their other children while simultaneously advocating for services and trying to protect their child from systems and experiences that threaten further harm.

Patients whose functioning is dramatically compromised or whose choices are dictated by geography or their HMO are not often able to leave one provider to find another more responsive one. The illness itself can prevent self-advocacy. Individuals who do not have a family member or friend to assist with coordination of care, research, and advocacy are severely limited in their ability to secure appropriate medical intervention, which may lead to a sense of hopelessness and desperation, followed



by depression and even suicide. Patients who experience plummeting financial security and lost earning potential are also vulnerable to homelessness.

## Systemic Barriers

The most avoidable and detrimental limitations to patient access to appropriate and affordable care are interdependent systemic barriers, which cause much of the stress and suffering described previously.

### CDC Surveillance Criteria

As detailed in chapter 2 on Epidemiology and Ecology, the inappropriate use of the CDC surveillance criteria for Lyme disease diagnosis is of particular concern to patients, especially in states where Lyme disease is considered to be “low incidence” despite significant evidence to the contrary. Medical providers in low-incidence regions frequently do not consider Lyme disease and other tick-borne diseases in their differential diagnoses. As a result, their patients are not diagnosed early, are at risk for developing chronic disease, and must travel to “high incidence” states to seek treatment.

Compounding the problem, insurance companies routinely use the CDC surveillance case definition as the recognized clinical criteria for diagnosis and subsequent treatment. They, therefore, deny coverage and treatment reimbursement for patients who do not meet the criteria. When these patients find themselves without options, they are vulnerable to the exploitation of unscrupulous practitioners offering costly and ineffective treatments.

## IDSA and ILADS Guidelines

Clinicians encounter systemic barriers as well. The medical opinion on diagnosis and treatment of tick-borne diseases is divided into two schools of thought, each described in a set of guidelines: (1) the Infectious Diseases Society of America (IDSA) and other medical societies, and (2) the International Lyme and Associated Diseases Society (ILADS). The IDSA guidelines promote the diagnosis of Lyme disease through recognition of more specific objective manifestations of disease and confirm the diagnosis by two-tiered serologic testing, except in cases of early Lyme disease with the erythema migrans rash, which constitutes a clinical diagnosis. The IDSA guidelines usually recommend 10 to 21 days of antibiotic treatment, except in cases of late arthritis where it may be longer. In contrast, the ILADS guidelines promote the use of clinical judgment with an emphasis on both signs and symptoms of disease when diagnosing and treating tick-borne diseases and do not restrict the long-term use of antibiotics.

Despite the existence of two peer-reviewed, evidence-based treatment guidelines, there is an apparent governmental and insurance industry bias for use of the IDSA standards and guidelines exclusively. Physicians who choose to follow the ILADS guidelines are often criticized by other physicians and penalized by state medical boards, causing many providers to avoid treating chronically ill patients.

### Managed Care and HMOs

Another obstacle to affordable care is the managed care and HMO system. The majority of doctors referred to as “Lyme-literate” are typically not part of managed care systems due to imposed compliance with insurance guidelines



for care and low levels of reimbursement for the time spent with patients. Those clinicians are largely inaccessible to patients who must obtain care within their provider group. Patients with resources to seek care outside their HMO, or who are covered by preferred provider medical insurance plans, may seek treatment from a Lyme-literate doctor. However, those doctors most often do not directly bill insurance companies, leaving the patient to pay for care out of pocket, incur higher co-pays, and submit claims to the insurance companies for reimbursement.

Attempts to claim reimbursement for services are fraught with detours and often fail. Initial rejection of claims is common, followed by long hold times on the telephone trying to get assistance from the insurance carrier, cumbersome documentation, and required resubmission of claims. When patients are severely ill, some with neurological issues, managing the reimbursement, claims, and appeal processes is grueling. The necessary sustained tenacity, tracking and recordkeeping, and potential additional costs are often not possible for people facing a multitude of symptoms, which may include neurological processing deficits and exhaustion. Without an advocate or family member to assist, patients sometimes report “giving up,” feeling that they are not capable of fighting for reimbursement while also fighting for their health. This further contributes to their financial vulnerability and may obstruct their ability to obtain the doctor-recommended treatment.

Those patients who are not rejected outright are still faced with long authorization periods for treatment and specialized medications not on the general formulary. This delay in treatment can have detrimental impact on the healing process of the patient.

## Institutional Discrimination

Another major concern for patients, their loved ones, and patient advocacy groups is the presence of underlying institutional discrimination, including conscious and unconscious biases against treating late-stage and chronic Lyme disease and complex cases of tick-borne disease. Institutions designed many decades ago are ill-equipped today to deal with the complexities of tick-borne disease. This results in systemic failures and institutional discrimination in both the employment and educational arenas. Such bias and discrimination further exacerbate today’s challenges and negatively impact health outcomes, socioeconomic status, and the overall quality of life for patients and their loved ones.

## RECOMMENDATIONS

The Working Group identified the following recommendations that the Federal Government could initiate to significantly improve patient access to care and health outcomes.

### **Recommendation 6.1: Create a federal repository for information on Lyme disease and other tick-borne diseases.**

Education is a vital first step in the prevention of Lyme disease and other tick-borne diseases. Patient advocacy groups play a major role in educating the public, patients, and providers and devote significant resources to this effort. However, their services vary widely from state to state, leaving those in non-endemic areas in particular without valuable information and educational opportunities. Information provided by state agencies is equally inconsistent.

Thus, a federal repository for accurate, up-to-date information on Lyme disease and other tick-borne diseases is warranted to allow for the dissemination of consistent messaging throughout the United States.

## Public Education

Public education requires circulation of information through numerous channels. Many patient advocacy websites provide free access to up-to-date curriculum for teachers, outdoor educators, science teachers, health educators, students, and parents. Advocacy groups and organizations also host local community education events and conferences with speakers and exhibitors. They organize workshops and continuing medical education conferences for medical providers and mental health clinicians to help bring awareness of tick-borne disease up-to-date. Many of these organizations are the mouthpieces for research, publicly sharing the latest diagnostic tools and treatment options along with information about newly discovered strains of tick- and vector-borne diseases, while some also directly fund research on Lyme disease and other tick-borne diseases.

Educating the public is multifaceted and includes individual education, as well as how to translate what works for individuals into community solutions at the local, regional, state, and national scales. The public needs information about

- What symptoms to look for;
- The positives and negatives of sending ticks for testing and where to send them;
- How and where to seek a medical provider who is knowledgeable about tick-borne diseases;

- The challenges associated with testing;
- What test(s) to ask for and what treatment options exist;
- How to find help when faced with various forms of discrimination due to tick-borne diseases; and
- How to obtain accurate, up-to-date knowledge in dealing with a tick-borne disease.

According to the CDC, children ages 5 to 14 are a high-risk population. Children require age-appropriate materials to protect themselves from ticks and tick-borne disease. School educators and nurses need more in-depth education on prevention, recognition of symptoms, and awareness of exposure. Some states considered endemic have developed education curricula on tick-borne diseases. For example, New Jersey encourages districts to adopt their state-developed curricula and requires annual training for teachers who instruct students with Lyme disease. These could be adapted for school systems in other regions all across the United States. While educational interventions to reduce Lyme disease among at-risk school children have had little attention and warrant further research, one study found that a short in-class educational program can improve knowledge, attitude, and self-reported precautionary behavior among at-risk children (Shadick et al., 2016).

## Patient Education

Through education and greater awareness, patients and the community at large can be taught the differences between the various tick-borne diseases and where they occur; which diseases different ticks are known to carry; and



how to recognize signs and symptoms. Many public health offices disseminate information about ticks and prevention; however, the breadth and depth of this information, if any at all, varies from state to state. Most primary care providers do not customarily offer information about support group meetings and resources to Lyme disease and tick-borne disease patients like they would for cancer or diabetes patients. Advocacy groups and organizations are the frontrunners in sharing this information directly with patients and the public.

## Clinician Education

The complexity and controversy of tick-borne disease(s) discourages many health care providers and clinicians from even attempting to treat patients with Lyme disease and other tick-borne diseases. This results in a shortage of health care providers who are willing and sufficiently trained to treat patients. Compounding the issue, some educational programs and authoritative sources disseminate inaccurate information, which is easily shared on the Internet. Moreover, many practitioners are unable to recognize and then distinguish tick-borne diseases in their various stages (Hirsch et al., 2018).

Clinician education in the U.S. medical system is further complicated by a divide between physical health and mental health. Tick-borne diseases can have neuropsychiatric manifestations and may result in referrals to mental health providers who have not yet learned to consider tick-borne disease. While mental health professionals might assist patients in strengthening their ability to cope with the distress of their disease, psychotherapy and counseling will not result in the treatment of the underlying illness. However,

it should be noted that patients sometimes do require psychiatric intervention or counseling in addition to medical treatment for their tick-borne diseases.

Both medical and mental health professionals need to be better trained to understand patients who suffer from infection-induced neuropsychiatric and neuropsychological symptoms, working together in a coordinated, multidisciplinary, treatment-team approach that utilizes the relevant expertise of these respective fields. Failure to identify a covert medical illness such as a tick-borne disease inadvertently delays the patient's diagnosis and subsequent treatment, which can have dire consequences.

Physician and clinician training for tick-borne diseases may be improved through two primary avenues:

1. Curricula taught and tested in medical school, in teaching hospitals, and by the United States Medical Licensing Examination to earn a U.S. license; and
2. Continuing medical education (CME) credits that physicians must annually complete in order to maintain their U.S. licenses.

Some medical associations and advocacy organizations host scientific conferences where physicians can earn CME credits. Still, more education programs are needed for tick-borne disease, especially high-quality and rigorous programs that are

- Frequently updated with the latest science and emerging technologies;
- Peer-reviewed to satisfy the highest medical and scientific standards;

- Free of charge; and
- Openly available online or otherwise, so that educational materials are easily discoverable, accessible, and free to use by all stakeholders.

Some organizations provide grants and funding for education programs offered by hospitals, universities, and other institutions. These venues provide an opportunity for researchers to report latest discoveries, exchange hypotheses, and form research collaborations. Patients sometimes also attend these conferences, which offer opportunities to network and learn about providers, testing, treatment options, and cutting-edge science that can benefit clinicians and other stakeholders.

### **Recommendation 6.2: Allocate increased funding for tick-borne disease in the areas of research, treatment, and prevention proportional to the burden of illness and need.**

Lyme disease and other tick-borne diseases receive significantly less funding than other major illnesses that pose a similar level of risk and burden to the American public. Therefore, an increase in funding for research, treatment, and prevention is warranted to match the burden of tick-borne illness.

### **Underrepresented and High-Risk Populations**

Certain segments of the population are particularly vulnerable to tick-borne disease for a variety of reasons. They should be of special consideration when allocating funds for research, treatment, and prevention.

### **Children**

Children are one of the highest-risk groups for contracting tick-borne diseases. Families may be especially hard hit when more than one child is ill because they face higher medical costs and time lost at work for caregiving. In addition to the need for financial resources, there is tremendous need for enlightened academic services and accommodations for children in schools.

Students with tick-borne diseases experience severe disruption in their education (D.T. Dennis, personal communication, September 2, 1992). Not only do they struggle with frequent non-specific symptoms, such as forgetfulness, difficulty concentrating, and falling behind in their schoolwork, they also experience tangible challenges such drops in their grade point averages and loss of friends. The median duration of school absence is equivalent to more than one-half of the school year. And in many cases, the time is broken up, so that disruptions occur throughout a school year or years.

When the underlying infectious illness is unrecognized or poorly understood, students are at risk for misdiagnosis with a primary psychiatric disorder or learning disability, including attention deficit disorder, school or social phobia, and oppositional defiant disorder. These misdiagnoses overlook or ignore critical symptoms such as pain, fatigue, sleep deprivation, sensory sensitivities, and processing issues, each of which may impair attention and impede academic progress. The unpredictable course of the illness, including day-to-day fluctuations in its symptoms, challenge the typical service plans in place for students with learning disabilities or with illnesses that have a more predictable course or defined endpoint.



## ACCESS TO CARE, PATIENT OUTCOMES

School field trips into Lyme disease-endemic areas and playgrounds place children at risk for contracting Lyme disease. Prevention and awareness measures must be implemented in these situations, including, but not limited to, appropriate notification and balanced information regarding risk and prevention provided to parents and supervising staff members.

### **Pregnant Women**

Gestational tick-borne disease can be transmitted to unborn children *in utero* and has the potential to cause premature labor and fetal death.

One priority research area involves the risks of maternal-fetal transmission for various tick-borne diseases, as well as how to treat this population if exposed during pregnancy and needing treatment while pregnant.

### **Behavioral Health Patients**

Thousands of articles show associations between infections and neuropsychiatric manifestation of illness. At least 400 articles support the association between tick-borne disease and neuropsychiatric disorders, which includes, but is not limited to, depression, anxiety, bipolar disorder, cognitive impairments, and psychosis. Other research has addressed the immunological and neurological mechanisms by which the Lyme disease bacteria, *B. burgdorferi*, may cause neuropsychiatric symptoms.

Patients who experience Lyme disease-induced neuropsychiatric symptoms are at risk for misdiagnoses with primary psychiatric disorders. Given the challenges with diagnostic testing (See chapter 3 on Diagnosis), physicians sometimes fail to identify a medical explanation for a patient's physical symptoms and erroneously

attribute them to emotional factors, such as anxiety or depression. This results in inadequate medical treatment and also adds to the patient's distress and despair. Many of these patients bounce between hospitalizations in psychiatric and medical facilities and receive little appreciation for the infectious etiology of their neuropsychiatric symptoms. This disrupts continuity of care and results in a fragmented approach to complex, multisystemic illnesses. There is a need for dual-diagnosis inpatient units equipped to treat patients with infection-induced neuropsychiatric symptoms.

### **American Indian and Alaska Natives**

The Indian Health Service (IHS), an agency of HHS, is primarily responsible for providing health services to American Indians and Alaska Natives. IHS is chronically underfunded and often not able to provide all health services available to the general populations. Moreover, the health care facilities that could provide the needed services are located in rural and remote areas and often hours away from patients by car.

IHS alignment with recommendations in this report for VA, CMS, and DoD (see Recommendation 6.3(c), page ##) would improve care to American Indian and Alaska Natives for tick-borne disease. IHS opportunities exist to upgrade processes and improve employee education through interoperable diagnostic codes, standardized medical coverage, and reimbursement policies for tick-borne disease. IHS systems with health records that interface seamlessly with other federal agencies would improve care and coverage on tribal lands, ensuring consistent medical care and coverage for everyone.

### ***Military Servicemembers, Military Families, and Veterans***

Continuity of care is vital to accurately diagnosing and adequately treating chronic Lyme disease and tick-borne diseases. Because the military is under-resourced and understaffed, many military Servicemembers and their families do not receive consistent care over time with the same provider. Military medicine is well-suited for acute, easy-to-diagnose illnesses, injuries, and infections. It is not well-suited for chronic or complex conditions because both families and medical providers are regularly deployed and moved to different locations.

Military Servicemembers, their families, and Veterans are a high-risk population due to exposure of global species and strains of tick-borne disease. In the case of Veterans, they may be medically separated or retired with undiagnosed or misdiagnosed diseases. For examples of such scenarios, see the patient profiles of Veteran Ruben Lee Sims (page ##) and medically-retired Colonel Nicole Malachowski (page 70). Unless Veterans reach the 20-year pension mark, which allows them more choice in medical providers, Veterans are dependent on the Veteran's Administration's health care system. As such, they are subjected to the same federally endorsed criteria and guidelines for diagnosing and treating Lyme disease and other tick-borne diseases that are being called into question in this report.

### ***Hispanic or Latino Populations***

According to the U.S. Department of Labor, Hispanic or Latino populations comprise 43.1% of grounds maintenance workers and 44.3% of workers in farming, forestry, and fishing industries,

leading to higher rates of exposure to ticks and potentially tick-borne diseases ("Labor Force Statistics from the Current Population Survey," 2017). Compared to other populations, one study showed that Hispanics or Latinos displayed signs of disseminated infection and symptoms onset during the fall at a significantly higher rate. Placing this group at further risk, only 58.5% were reported as having health insurance during the 2009 to 2013 period compared to 84.9% of non-Hispanic or Latino whites. Moreover, 15.5% of Hispanics or Latinos studied reported not seeking or delaying medical intervention (Nelson, Starr, Kugeler, & Mead, 2016).

### ***Migrant Workers***

Due to outdoor working habits, migrant workers are at high risk for exposure to tick-borne diseases. With limited or no health care, they often lack the means for adequate diagnosis and proper treatment.

### ***Hunters, Hikers, Golfers, and Outdoor Enthusiasts***

Those with outdoor occupations or avocations are at increased risk. A healthy outdoor lifestyle can increase exposure to ticks and risk for tick-borne disease, especially without proper precautions in high-risk regions (see chapter 2 on Epidemiology and Ecology and chapter 3 on Prevention). This high-risk population includes hunters, hikers, golfers, anglers, park rangers, campers, landscapers, and others who spend significant time outdoors.



**Recommendation 6.3:** Ensure the rights of those dealing with Lyme disease and tick-borne diseases and conditions by reducing the burden of the processes under which patients are currently diagnosed and treated and by which they access care. Basic protections must include, but not necessarily be limited to, those that:

**6.3(a):** Protect patients from employment discrimination.

The highest risk of exposure to Lyme disease and other tick-borne diseases falls on people who work outside in regions where ticks are known to occur. Those individuals make up the majority of workers who file compensation claims for tick-borne disease contracted on the job; however, even employees who work in urban areas, far from tick habitats, occasionally file tick-borne disease compensation claims as well (Cohen, 2004).

The case of *Grano v. Long Island R. Co.* (1993) serves as an example of an attempt by an employer to deny its employees compensation for disability resulting from job-related tick-borne disease. In this case, four workers brought an action against their employer, the Long Island Railroad Company (LIRR), claiming that they had developed Lyme disease after encountering ticks at various Suffolk County, New York, work sites over a two-year period. The court ultimately decided in favor of the plaintiffs, ruling that the LIRR was in breach of the Federal Employer's Liability Act (FELA) requirement for employers to maintain and inspect work areas and "provide workers with a reasonably safe workplace" (Cohen, 2004). The judge on the case ("*Grano*

*v. Long Island R. Co.*, 818 F. Supp. 613 (S.D.N.Y. 1993)," 1993) stated:

The railroad knew or should have known . . . of the tick infestations and of the risk of infection. . . . All four plaintiffs were assigned to work in tick-infested areas . . . and within weeks or months . . . manifested symptoms of Lyme disease. All were subsequently diagnosed as having Lyme disease. The Lyme disease contracted by all four plaintiffs was caused by their working in unsafe areas where they were doing their jobs, as they were required to do, in connection with their employment by defendant LIRR.

As demonstrated by this case, the Federal Government should ensure that existing workers' compensation laws protect workers who have contracted tick-borne disease on the job from denial of insurance compensation claims. In addition, existing laws that provide for reasonable accommodations under the Americans with Disabilities Act (ADA) must be enforced for those workers who are ill due to Lyme disease and other tick-borne diseases.

**6.3(b):** Protect students of all ages from discrimination.

Students with Lyme disease all too often face the added burden of needing to convince school authorities of the reality and credibility of their ongoing illness. They require flexible attendance policies without fear of truancy charges. Existing models of accommodations provided in 504 plans and individualized education programs (IEPs) are often not suited for children with tick-borne disease. Current educational systems often



present the options of either school attendance or home instruction. However, hybrid and creatively designed plans are necessary to provide opportunities for the richest and most “normal” growth and development for children who live with myriad symptoms that wax and wane, even over the course of a day, and compromise their ability to fully engage in mainstream education.

Socialization is an essential part of child development. Children who have not attended school are sometimes faced with punitive measures, such as exclusion from after-school activities. Preventing them from engaging in meaningful socialization with their peers is punishing, isolating, and intensifies the emotional pain and loss of normalcy. Further, the longer a young person is at home and outside the peer environment, the more difficult it may be to reenter. This isolation may result in unintended social and emotional consequences that compound the challenges the young person faces.

The Department of Education (DoED) should examine its policies and procedures to ensure that individuals with Lyme disease and other tick-borne diseases are protected from discrimination in schools, especially in the area of 504 compliance and IEPs. This involves protecting and enforcing the rights of these students under the ADA. DoED should investigate to determine if all such policies and procedures are being adhered to throughout the United States and needs to proactively communicate that Lyme disease and tick-borne diseases fall under anti-discrimination laws, such as existing laws that guarantee a Free and Appropriate Education (FAPE) for students with tick-borne diseases under the Individuals with Disabilities Education Act (IDEA).

### **6.3(c): Protect patients from health care and disability insurance coverage and reimbursement policies that are unduly burdensome.**

As detailed in the Systemic Barriers section, insurance companies regularly deny medical care to tick-borne disease patients who do not meet the CDC surveillance criteria for Lyme disease. Until new laws are passed, private insurance companies cannot be required to cover Lyme disease and other tick-borne diseases. In the interim, the Federal Government is urged to change its own systems and lead by example.

### **Health care, Health Insurance, and Disability Coverage**

Federal providers of health care and health insurance—beginning with VA, CMS, and DoD—need to standardize and streamline reimbursement policies for tick-borne disease. Diagnostic coding should be standardized across all federal systems, so that patient records and reimbursement processes are more easily navigable and consistent for everyone, including Servicemembers, Veterans, and civilians.

Federal benefits for people with disabilities should be similarly streamlined and improved, so that claims are consistently processed without unduly burdening those disabled by tick-borne disease. The Federal Government can achieve this by, first, recognizing the severity of tick-borne disease and, second, mapping the disabling consequences of tick-borne disease to DoD, VA, and U.S. Social Security Disability Insurance (SSDI) programs. Institutional recognition that tick-borne diseases can disable some—with measurable criteria and codes for disabilities related to tick-



borne disease—will expedite processing and, for those who qualify, receipt of earned benefits.

## Shared Medical Decision-Making and Patient-Centered Care

Beyond federal health care and insurance programs, the Federal Government can lead by example with patient-centered care. This approach focuses on shared medical decision-making, which takes into account the individual circumstances and values of the patient. It is particularly important when the evidence base is uncertain. Patient involvement is also critical to making the “right choice” when different combinations of treatment options, uncertain outcomes, and implicit trade-offs exist. Under shared medical decision-making, clinicians are viewed as experts in the evidence, and patients are the experts in what matters most to them.

No single diagnostic and treatment program for Lyme disease is universally successful or accepted, causing significant uncertainty. When more than one set of guidelines exists (ILADS and IDSA), the question then becomes who decides the appropriate course of treatment for the patient. Under the medical ethical principle of autonomy, the treatment decision belongs to the patient in consultation with his or her provider. Thus, the American Medical Association requires that the physician disclose and discuss with the patient the risks and benefits of the proposed treatment and also the risks and benefits of available alternative treatments.

The legal doctrine of informed consent requires physicians to inform patients of existing treatment options, their probable outcomes, and the risks and benefits associated with each. For a patient who may be too ill to work or attend school,

the potential benefits of treatment may well outweigh the risks. It is essential that patients be provided the right of informed consent, including information on the limitations of current diagnostics, and the authority to decide which of the available treatment options they wish to follow.

Federal momentum already exists to empower patients to share in their own health care decisions. CMS, in conjunction with the White House Office of American Innovation (OAI) and VA, has implemented MyHealthEData, which allows patients to choose the provider that best meets their needs and then give that provider secure access to their data, leading to greater competition and reduced costs. Through MyHealthEData, patients receive an electronic copy of their entire health record, which they can share at their own discretion. Patient-centered tools such as this allow patients to address their own unique health care needs, have a better understanding of their overall health, prevent disease, and make more informed decisions about their care.

**6.3(d): Protect the rights of licensed and qualified clinicians to use individual clinical judgment, as well as recognized guidelines, to diagnose and treat patients in accordance with the needs and goals of each individual patient.**

In endemic states, many providers who treat persistent Lyme disease and other tick-borne diseases with long-term antibiotics risk their livelihoods and reputations to do so. Other clinicians accuse them of compromising the health of the patient, and state medical boards prosecute them for operating outside the IDSA

guidelines. These prosecutions have led doctors to feel hesitant about handling chronic or recurrent cases, forcing patients in some instances to seek treatment beyond their home states.

The IDSA guidelines for treating Lyme disease (Wormser et al., 2006) contain a footnote with the following statements:

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.

Despite the footnote, state licensing boards subject medical providers to disciplinary action and fines for choosing to determine the direction of their patients' treatments based on their clinical judgment, other recognized diagnostic and treatment guidelines, individual circumstances, and previous treatment responses. Therefore, it falls on each state to produce legislation or policy solutions to promote public awareness and protection for patients and providers. Advocates have successfully achieved those solutions in several states to date, although legislative solutions should be a last resort, since once passed, they are seldom repealed.

## Major Issue 6.4—Testing and Diagnostic Bands: How They Are Used Today and What That Is Doing to Patients

### Empower Patients with Data

As previously discussed in chapter 4 on Diagnosis (pp. #), the western blot results and reporting for Lyme disease can be problematic for patients and clinicians because laboratories report only western blot bands used in CDC surveillance criteria. Most laboratories will not report the other bands, such as the 31 and 34kDa positions, which could potentially reveal diagnostic information to clinicians, especially to those who have patients with equivocal western blot test results. Laboratories have latitude on how to display results, and some claim that federal regulations restrict them from releasing all western blot results. Congress and the HHS Secretary could direct the FDA to update and clarify its requirements on western blot tests for Lyme disease, explicitly allowing patients to access their own health data, including their own laboratory results. This direction aligns with societal and government-wide initiatives to empower patients to access, control, share, and use their own medical records and health care information. Data-driven decisions are key to improving their health outcomes.

### Engage Diverse Stakeholders—Update the CDC Surveillance Case Definition with 21<sup>st</sup> Century Evidence

Data collection and scientific understanding have evolved since the 1994 Dearborn conference (see chapter 4 on Diagnosis), yet Lyme disease diagnostics and surveillance criteria remain unchanged. It is time to revisit the Dearborn

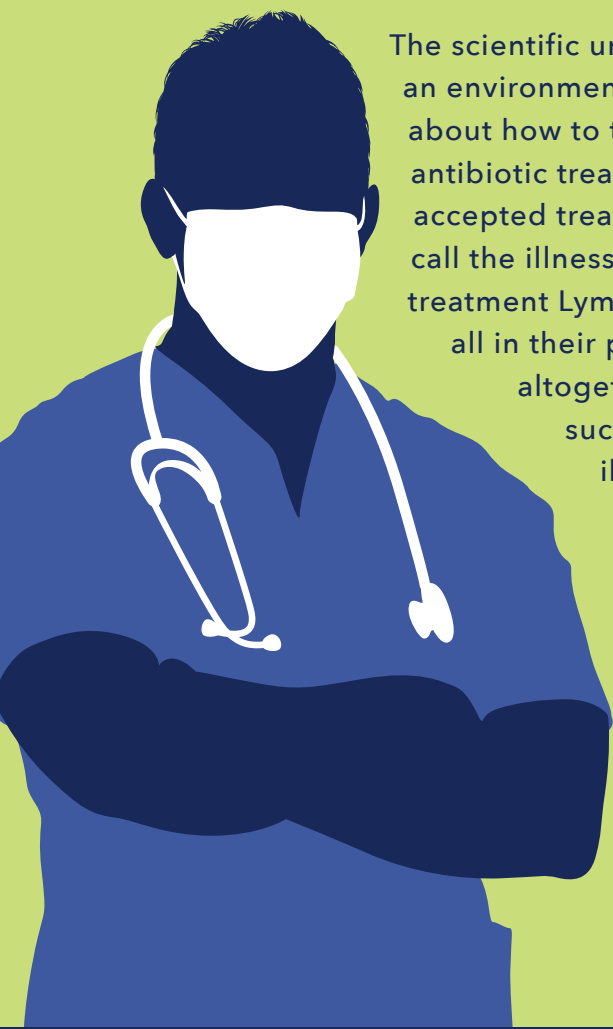


conference outcomes by convening a meeting of all relevant stakeholders—including government scientists, academic researchers, industry leaders, treating clinicians, patients, family members, and advocates—to review the evidence and interpretive criteria using all of the newest diagnostic methodologies, techniques, technologies, and emerging science. Diverse stakeholders, the working group, CDC, NIH, FDA, and CSTE could examine the science and “real-world evidence”—including clinician data and patient registries—to co-create new outcomes and criteria that supersede outdated ones.

## Relay Information as a Neutral Knowledge Broker

The Federal Government cannot endorse one set of treatment guidelines over another, yet it can clarify the intended purpose of its surveillance criteria and recognize all third-party guidelines that meet pre-defined standards and criteria. Agencies act as a neutral knowledge broker of evidence-based clinical practice guidelines and related documents. Historically, the National Guideline Clearinghouse (NGC) served this purpose by providing one government website with free online access to all guidelines that meet pre-defined standards for treating tick-borne disease. As of July 2018, however, NGC funding was discontinued, and this resource is no longer available to practitioners and patients. Science and guidelines have not changed; they are simply no longer easily accessible from a trusted government website. As a result, some physicians and patients face increased difficulty to justify their medical treatments and insurance reimbursements. This working group or other federal agency could create a webpage with resources and links to all guidelines (for example, those on the former NGC website) that meet pre-defined standards for diagnosis of tick-borne diseases and conditions.

# Challenges Facing Physicians and Impeding Patient Access to Care



The scientific unknowns and strongly held, differing views have created an environment where many physicians are confused and uncertain about how to treat their patients with chronic symptoms after standard antibiotic treatment of Lyme disease. For those patients, no uniformly accepted treatments exist. Physicians cannot even agree on what to call the illness: Some call it chronic Lyme disease; others call it post-treatment Lyme disease syndrome; and still others claim the illness “is all in their patients’ heads.” Many physicians avoid the controversy altogether by choosing not to provide continuity of care for such patients. Some are reticent to speak up about the illness, worrying that they may risk their medical licenses, career, and credibility for doing so.

This report does not represent a particular stance on these issues; rather, it recognizes the legal challenges as a barrier to patients’ access to care. Patients bear the brunt of this situation when their doctors are caught up in these issues, and they risk losing their trusted physicians. It is time to reexamine the U.S. system of care and payment for this vulnerable group of patients.

**Patients and the stakeholder community are core to the Working Group process and essential for its success—and, most importantly, for improved patient outcomes with tick-borne disease. Diverse perspectives fuel scientific breakthroughs, innovation, and collaborations to co-create solutions.**





# Patient Stories

## Julia Bruzzese and Family



### Julia Bruzzese

High School Sophomore  
Pediatric Lyme disease Patient and  
Lyme Disease Advocate  
Brooklyn, New York

Julia Bruzzese was a lively nine-year old when she was bitten by a tick and contracted Lyme disease, associated coinfections, and other types of tick-borne diseases ("Lyme"). Although she was brought to the pediatrician with a bullseye rash after the tick bite and for many subsequent sick visits, Julia went undiagnosed for more than two years. She is now 15-years-old and bound to a wheelchair due to her on-going battle with the Lyme. After Julia received extensive serological workups for every possible diagnosis on numerous occasions, and despite Julia was suffering from early signs of Lyme and increasingly worsening symptoms, doctors failed to make an accurate diagnosis and provide her with timely treatment. Because of a lack of reliable diagnostic testing, doctors and hospitals did not diagnose or treat Julia for Lyme disease, and insurance companies refused to pay for the expenses. As a result, Julia eventually lost her ability to walk, among many other things, and nearly died at age 11.

While Julia's health was declining, other members of the Bruzzese family (Julia's parents, older brothers, and little sister) realized they were all suffering from many symptoms similar to Julia's. However, the family's focus and dwindling financial resources were allocated to Julia, the sickest one. They were determined to save Julia's life, to get her childhood back, and to seek an answer and hope.

Hope came after Julia met Pope Francis in 2015. The Papal Blessing drew international attention and increased awareness. Love and support began pouring in. Julia was subsequently diagnosed with Lyme, bartonellosis, and babesiosis. All Bruzzese family members were diagnosed with Lyme as well.

With the financial support raised by her community and other parts of the world, Julia and her family received treatment from physicians experienced with Lyme disease. The family saw tremendous improvement after the proper treatment and Julia's symptoms gradually improved. Because treatment was delayed for so long, Julia, however, still suffers from the chronic effects of Lyme and remains in a wheelchair.

**"It is not fair that many share my story of suffering and a life being lost. I am determined to bring about change, and bring hope to those who have forgotten the meaning of the word."** - Julia Bruzzese, age 15

**"I fear for her life and feel like a soldier stationed by her side to protect her, guide her, and mask her from the nightmare that we're living."**  
- Enrico Bruzzese, father

**"One day, I'll have my sister back."**  
-Sophia Bruzzese, sister, age 9

**"Where medicine fails, love for my children will prevail."** - Josephine Bruzzese, mother

**"We are all being put to the test, pushed to the limit to reveal how far we go."** - Adam Bruzzese, brother, age 17



# Looking Forward

## Recommendation At a Glance: Looking Forward



**Recommendation 1: NIH:** Create an NIH tick-borne disease strategic plan, with public input during creation and implementation, to address tick-borne diseases, including all stages of Lyme disease. Include in the strategic plan the coordination of research funding across NIAID, NINDS, NIAMS, and NIMH to increase knowledge of pathogenesis, improve diagnosis, and develop and test new therapeutics for tickborne diseases. Update every five years.



**Recommendation 2: CDC:** Dedicate funding within CDC to study—with performance indicators—babesiosis incidence, prevalence, treatment resistance, and prevention, including maternal-fetal and transplantation/transfusion transmission risk. Consider using advanced data tools, such as patient registries, to study the potential role of *Babesia* in tick-borne disease patients with continuing manifestations of disease after initial treatment.



**Recommendation 3: DoD:** Commence study of tick-borne disease incidence and prevalence of active duty Servicemembers and their dependents. Compile data on the impact of tick-borne diseases on military readiness. Create education and preparedness programs that specifically address the unique risks faced by Servicemembers in training and on deployment and by their families.



**Recommendation 4: VA:** Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members.



**Recommendation 5:** Develop and disseminate more comprehensive clinician education that highlights diverse symptomology, expanding geography of infecting ticks, and limitations of current testing procedure. In developing the curriculum, include diverse stakeholder groups, including clinicians, research scientists, and patients who represent the spectrum of scientific and medical expertise and perspectives on tick-borne disease.



## LOOKING FORWARD

The challenges posed by Lyme disease and other tick-borne diseases have been increasing in scope and complexity in recent years. Problems caused by these illnesses cannot be solved with a single or narrow approach. Solutions must be interdisciplinary, evidence-based, and data-driven. They require a comprehensive and flexible public health response—across silos, disciplines, institutional boundaries, and conventional norms. If we are to effectively and efficiently address tick-borne diseases in the United States, we must engage all of the diverse stakeholders and strategically move forward together. A diversity of perspectives can help us unlock scientific breakthroughs and improve policy by harnessing the power of emerging technologies, methods, and insights from seemingly unrelated fields. It also fuels novel exploration, innovation, and the co-creation of solutions through information sharing (for example, open data and open science) and collaboration techniques for open innovation (for example, crowdsourcing, citizen science, prizes, challenges, and innovative public-private partnerships). All of these must be undertaken through channels that promote and safeguard scientific and methodologic rigor.

As part of an ongoing six-year process, this report is a first step in transforming the United States response to tick-borne diseases. Success is not measured by the number of recommendations in this report, but rather by improved patient outcomes due to concrete actions taken by Congress, HHS, and other Federal agencies. In two years, when the next report is due in 2020, the Working Group hopes and expects many recommendations will have been acted upon.

It is no easy task to tackle thorny scientific and political quagmires that have divided stakeholders for decades. If it were easy, many of today's tick-borne disease challenges would be closer to being solved. Much work remains, amidst great scientific uncertainty, yet we must move forward. The American people have demanded it. The American people deserve it.

Now is our time to start fresh by re-charting a new course in the history of tick-borne diseases where everyone has easy access to accurate diagnostics and affordable care that restores health. It is time for 21<sup>st</sup>-century solutions to make a difference through participatory medicine, which aligns clinicians, patients, and researchers to co-create next-generation solutions. This report is one step to getting us closer to this shared vision.

The working group of 14 members found substantial agreement on key concepts, even though everyone had different expertise and experiences with tick-borne diseases. Commonalities that emerged include the need for better U.S. surveillance data on where ticks are spreading, which diseases they carry, and how this translates into cases of human tick-borne diseases. The working group members unanimously and enthusiastically supported improved diagnostic tests for tick-borne diseases. Everyone also agreed that we must better understand the cause of persistent symptoms after initial treatment of tick-borne diseases. We may not have agreed on whether to call it “chronic Lyme disease,” “late-stage Lyme disease,” or “post-treatment Lyme disease syndrome (PTLDS),” yet we all agreed that individuals with persistent symptoms are legitimately sick and in need of medical care to alleviate suffering today. Americans with tick-borne disease need greater access to quality, affordable



patient care. The working group also found agreement around the need for increased education and prevention activities.

Looking to the future, report updates in 2020 and 2022 will further investigate U.S. issues surrounding tick-borne diseases. The Working Group expects that future reports will provide in-depth examination of priority issues identified during the 2017-2018 process, including but not limited to:

- Scientific literature reviews on tick-borne diseases in the United States.
- Federal research and activities related to tick-borne diseases across the Federal Government. The HHS, DoD, and VA inventory of activities from this report will be updated and new information included (if applicable) from additional agencies, departments, and offices.
- A strategic approach to public-private partnerships and collaborations, so that tick-borne diseases as a national priority will not only involve the Federal Government, but will also harness the power, resources, commitment, and innovation across all sectors—industry, academia, non-profit organizations, as well as local, state, and other governments.
- A systematic review of adverse effects from overdiagnosis and the use of unsubstantiated treatment for presumed tick-borne diseases.
- A systematic review of adverse effects from underdiagnosis and undertreatment for tick-borne diseases.
- A systematic review of unresolved priorities and questions, including:
  - ◇ Rising healthcare costs in the United States due to Lyme disease, other tick-borne diseases, and coinfections with multiple pathogens.
  - ◇ Nomenclature challenges such as chronic Lyme disease, neurological Lyme disease, late-stage Lyme disease, and PTLDS.
  - ◇ The shortcomings and limitations of vaccine and diagnostic clinical trials have.
  - ◇ The inclusion of vulnerable and high-risk populations in clinical trials, for example, children, pregnant women, and individuals with on-going symptoms who once had Lyme disease or other tick-borne diseases and, therefore, may respond to treatment differently than “healthy” adults.
  - ◇ Transmission unknowns.
- Incorporation of patient experiences into the conventional scientific approach, including the evaluation of information from patient registries and patient-powered research.
- Trust building. The Working Group cannot erase past events or rewrite the history that caused distrust of vaccines. However, we can acknowledge the past, learn from it, and do better by 1) working in collaboration with diverse stakeholders, 2) increasing transparency, and 3) ensuring that Federally funded research and activities serve the real-world needs of Americans.

Past differences and divisions in Lyme disease history will not go away overnight, yet together we can choose to reset and move forward to achieve one shared vision: ***A nation free of tick-borne diseases where new infections are prevented and patients have access to affordable care that restores health.***



## LOOKING FORWARD

The working group's takeaway message to Congress is: allocate increased funding for tick-borne diseases in the area of research, treatment, and prevention that is proportional to the burden of illness and today's need. Tick-borne diseases—beyond just Lyme disease—are a serious problem that is under-recognized. As a result, organizations devoted to tick-borne diseases are understaffed, and research and activities underfunded. Many recommendations in this report will require significant Federal investment—monetary, in-kind, and leadership resources—to advance research, policy, and education for tick-borne diseases commensurate with the scale and scope of the problem today.

The Executive Branch must strategically prioritize tick-borne diseases across many agencies and diverse programs to efficiently catalyze science and next-generation solutions. Given limited resources and high scientific uncertainty, we must ask: *How can the Federal Government accelerate science and develop answers as quickly as possible with the least cost to taxpayers?* In answer to this question, the Working Group identified recommendations to four Federal agencies. Each agency is critical to understanding the complexities of tick-borne diseases and identifying data-driven solutions.

- **Recommendation 1: NIH:** Create an NIH tick-borne disease strategic plan, with public input during creation and implementation, to address tick-borne diseases, including all stages of Lyme disease. Include in the strategic plan the coordination of research funding across NIAID, NINDS, NIAMS, and NIMH to increase knowledge of pathogenesis, improve diagnosis, and develop and test new therapeutics for tickborne diseases. Update every five years.
- **Recommendation 2: CDC:** Dedicate funding within CDC to study—with performance indicators—babesiosis incidence, prevalence, treatment resistance, and prevention, including maternal-fetal and transplantation/transfusion transmission risk. Consider using advanced data tools, such as patient registries, to study the potential role of Babesia in tick-borne disease patients with continuing manifestations of disease after initial treatment.
- **Recommendation 3: DoD:** Commence study of tick-borne disease incidence and prevalence of active duty Servicemembers and their dependents. Compile data on the impact of tick-borne diseases on military readiness. Create education and preparedness programs that specifically address the unique risks faced by Servicemembers in training and on deployment and by their families.
- **Recommendation 4: VA:** Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members.

Many recommendations in this report require systemic changes and possibly even paradigm shifts, depending on the outcomes of future scientific research. Other recommendations may be enacted immediately, without Congressional mandate, funding, policy action, or new scientific understanding. Examples include education and public outreach campaigns, which may be implemented now. They are critically important and cost-effective. With greater scientific knowledge and funding, their effectiveness and impact will only increase. Yet, we should not wait.

Education on tick-borne diseases must be an immediate national priority. Diverse stakeholders, including but not limited to the Federal Government, can:

- **Recommendation 5:** Develop and disseminate more comprehensive clinician education that highlights diverse symptomology, expanding geography of infecting ticks, and limitations of current testing procedure. In developing the curriculum, include diverse stakeholder groups, including clinicians, research scientists, and patients who represent the spectrum of scientific and medical expertise and perspectives on tick-borne disease.

U.S. leadership at the highest levels can help educate Americans about tick-borne diseases. For example, Congress or the President of the United States (through a Presidential Proclamation) could officially designate the month of May each year as Lyme Disease Awareness Month and/or Tick-Borne Disease Awareness Month. Such leadership would shine a spotlight on these illnesses and help bring more public awareness to existing outreach campaigns and prevention education by agencies. Education will be most effective if reinforced with consistent messaging across all levels of government, beginning at the top with the President, Congress, and the HHS Secretary.

The international community is looking to the United States for leadership, science, and innovation on how best to address tick-borne diseases. The United States is uniquely positioned to markedly change the course of tick-borne disease, especially Lyme disease, for the better. Our American innovation, science, creativity, and emerging technologies—including next-generation diagnostic platforms such as microfluidics, affinity capture technology, cytokine release assays, and nanopore sequencing—offer new hope for patients with Lyme disease and other tick-borne infections. A U.S. priority response with top Federal leadership and immediate investment would catalyze global attention and much-needed scientific research and development (R&D). It would also encourage industry, academia, and public-private partnerships to prioritize scientific R&D, education, and activities on tick-borne disease in order to decrease their societal burden and costs to public health care systems.

Domestically, Americans need Federal action now. In accordance with the six-year process established by the *21<sup>st</sup> Century Cures Act* of 2016, the Working Group aims to deliver a pragmatic path forward with recommendations for Federal actions to address tick-borne diseases. The immense challenge of tick-borne disease requires all hands on deck—all sectors, all disciplines, all of society—to co-create solutions as quickly as possible. We must do this together. And we must not stop working until our Working Group vision is an everyday reality for tick-borne disease patients in all 50 states.

# 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 that 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.



# Conclusion

The Tick-Borne Disease Working Group 2018 report is the product of a diverse group of stakeholders, including patients and patient advocates, government officials, physicians, scientists, and public health officials. The co-creation of this report brought this diverse group together (Appendix F), and they successfully produced the first-ever *21st Century Cures Act* report in the controversial field of Lyme disease and other tick-borne diseases in the United States.

This is one step in a six-year process, yet a remarkable feat. Although no process, nor report, is perfect, the Working Group sees our work during 2017-2018 as a major and positive step to changing today's status quo for the better. This report voices concerns from Americans, especially tick-borne disease patients, who demand change. It focuses on the key challenges of the emerging epidemic of Lyme disease and other tick-borne diseases facing the United States including:

- Tick ecology and the epidemiology of tick-borne infections;
- The prevention of tick-borne disease and the need for new strategies to prevent tick-borne disease;
- Diagnostic testing challenges;
- Treatment challenges, especially for patients with ongoing symptoms after initial therapy; and
- Challenges to patient access to care and outcomes in a field with much controversy.

Developing this report required listening and compromise in many areas with incomplete or conflicting science or data and differing opinions. It was a true collaborative project that built relationships and strengthened professional networks across silos. These will prove valuable and evolve further during the next four years as the report and recommendations are updated for Congress and the HHS Secretary.

Many of the recommendations in this report passed by unanimous consent. All members of the Working Group agreed that education is a priority, and that Americans with tick-borne diseases need federal action now. There were a few recommendations that had opposing viewpoints. In these cases, minority responses presented differing viewpoints.

At the highest level, the Working Group focused on the need for substantial increases in resources and funding for the urgent, unmet needs in research and patient care. For decades, tick-borne diseases have increased at an alarming rate—much faster than Federal R&D investments. As a result, the Federal Government today faces significant societal challenges and “research debt” due to the compounded costs over time that have—until now—been largely ignored without a comprehensive national response. The investments required now—just to catch up the United States in its understanding of tick-borne disease, as it does other public health threats like HIV/AIDs, Zika virus, and cancer—are substantial. Federal priority and investment must begin now.

The continued spread of ticks, the discovery of new tick-borne pathogens, and the spreading outbreak of human disease is a near certainty. This report lays out an initial analysis and recommendations in response to this public health crisis affecting hundreds of thousands of individuals each year in the United States.



# 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 2018 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.

### Working Group Members

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**Kristen Honey, PhD, PMP (Vice-Chair)**

Innovator in Residence, Office of the Secretary, U.S. Department of Health & Human Services; Senior Research Scholar, Stanford University; Member, Stanford University Lyme Disease Working Group

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## APPENDICES

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## Appendix B. List of Acronyms and Abbreviations

| Acronym/Abbreviation | Definition                                         |
|----------------------|----------------------------------------------------|
| <b>ADA</b>           | Americans with Disability Act                      |
| <b>CDC</b>           | Centers for Disease Control and Prevention         |
| <b>CME</b>           | Continuing medical education                       |
| <b>CMS</b>           | Centers for Medicare and Medicaid Services         |
| <b>COI</b>           | Cost of illness                                    |
| <b>CSTE</b>          | Council of State and Territorial Epidemiologists   |
| <b>DFO</b>           | Designated federal officer                         |
| <b>DoEd</b>          | U.S. Department of Education                       |
| <b>DoD</b>           | U.S. Department of Defense                         |
| <b>ELISA</b>         | Enzyme Linked Immunosorbent Assay                  |
| <b>EM</b>            | Erythema migrans                                   |
| <b>FACA</b>          | Federal Advisory Committee Act                     |
| <b>FAPE</b>          | Free Appropriate Public Education                  |
| <b>FDA</b>           | U.S. Food and Drug Administration                  |
| <b>FELA</b>          | Federal Employers' Liability Act                   |
| <b>GMO</b>           | Genetically modified organisms                     |
| <b>HME</b>           | Human monocytotropic ehrlichiosis                  |
| <b>HHS</b>           | U.S. Department of Health and Human Services       |
| <b>IDEA</b>          | Individuals with Disabilities Education Act        |
| <b>IDSA</b>          | Infectious Disease Society of America              |
| <b>IEP</b>           | Individualized Education Program                   |
| <b>IHS</b>           | Indian Health Services                             |
| <b>ILADS</b>         | International Lyme and Associated Diseases Society |



## APPENDICES

| <b>Acronym/Abbreviation</b> | <b>Definition</b>                                 |
|-----------------------------|---------------------------------------------------|
| <b>LIRR</b>                 | Long Island Railroad Company                      |
| <b>MMWR</b>                 | Morbidity and Mortality Weekly Report             |
| <b>NGC</b>                  | National Guideline Clearinghouse                  |
| <b>NICE</b>                 | National Institute for Health and Care Excellence |
| <b>NIH</b>                  | National Institutes of Health                     |
| <b>OASH</b>                 | HHS Office of the Assistant Secretary for Health  |
| <b>OspA</b>                 | Outer surface protein A                           |
| <b>OspC</b>                 | Outer surface protein C                           |
| <b>PCORnet</b>              | Patient-Centered Clinical Research Network        |
| <b>PCR</b>                  | Polymerase chain reaction                         |
| <b>PTLDS</b>                | Post-treatment Lyme disease syndrome              |
| <b>RNAi</b>                 | RNA interference                                  |
| <b>SFTS</b>                 | Severe fever with thrombocytopenia syndrome       |
| <b>SME</b>                  | Subject matter expert                             |
| <b>SSDI</b>                 | Social Security Disability Insurance              |
| <b>STARI</b>                | Southern tick-associated rash illness             |
| <b>VA</b>                   | U.S. Department of Veterans Affairs               |
| <b>WNV</b>                  | West Nile Virus                                   |

# Appendix C.

## C.1: CDC-Listed Tick-Borne Diseases in the United States

Anaplasmosis\*

Babesiosis\*

*Borrelia miyamotoi* infection

Bourbon virus infection (presumed to be tick-transmitted)

Colorado tick fever (CTF)

Ehrlichiosis\*

*E. chaffeensis* infection

*E. ewingii* infection

*E. muris euclairensis* infection

Heartland virus infection

Lyme disease\*

*B. burgdorferi* infection

*B. mayonii* infection

Powassan virus disease\*

Spotted fever rickettsiosis\*

*R. rickettsia* rickettsiosis (RMSF)

*R. parkeri* rickettsiosis

*Rickettsia* sp. 364D rickettsiosis

STARI (Southern tick-associated rash illness)

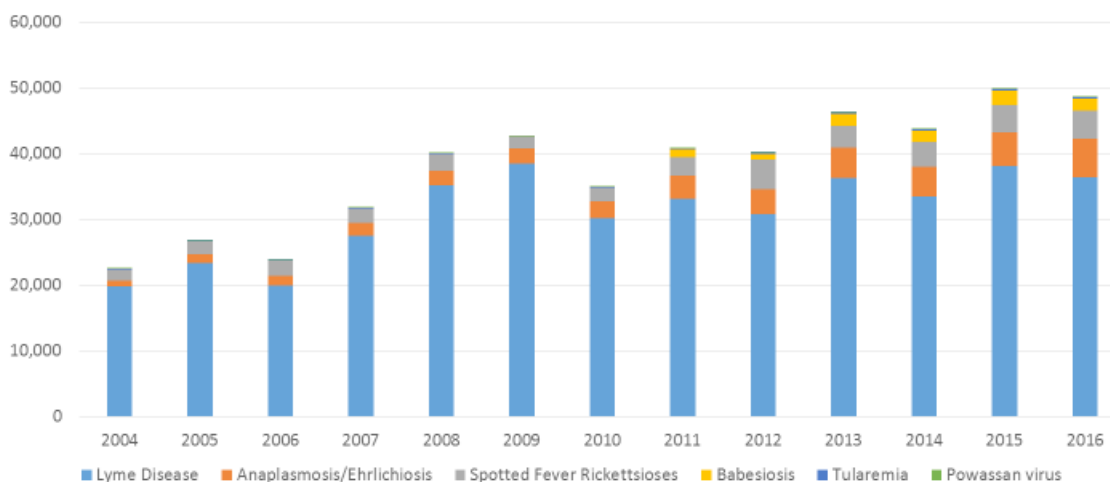
Tick-borne relapsing fever (TBRF) carried by soft ticks

Tularemia\*

\*Nationally notifiable to the National Notifiable Diseases Surveillance System

## C.2: Annual Reported Tick-Borne Disease Cases by Year, U.S.: 2004-2016

**U.S. Tick-Borne Disease Cases by Year, Reported Annually, 2004-2016**



Nationally Notifiable Diseases Surveillance System: <https://www.cdc.gov/nndss/infectious-tables.html>

Source: <https://www.cdc.gov/mmwr/volumes/67/wr/mm6717e1.htm>



## Appendix D. Inventory

### Tick-Borne Disease Working Group Inventory Analysis

According to the *21st Century Cures Act*, the Tick-Borne Disease Working Group was created to

1. Review all efforts within the U.S. Department of Health and Human Services (HHS) related to all tick-borne diseases;
2. Ensure interagency coordination and minimize overlap;
3. Identify research priorities and gaps.

To achieve these outcomes, the Working Group surveyed the following agencies about their roles and activities, if any, related to tick-borne diseases.

- The Centers for Disease Prevention and Control (CDC)
- The National Institute of Health (NIH)
- The Food and Drug Administrations (FDA)
- The Centers for Medicare and Medicaid Services (CMS)
- The Department of Defense (DoD)
- The Department of Veterans Affairs (VA)

All of the agencies responded to the inventory. However, CMS and VA did not report any program funding, research, or activity focused on tick-borne diseases.

### Agencies Overview

The Working Group sought to align the tick-borne disease activities within the agencies to the topic areas of the Working Group's six subcommittees: 1. Disease Vectors, Surveillance, and Prevention; 2. Pathogenesis, Transmission, and Treatment; 3. Testing and Diagnostics; 4. Access to Care Services and Support to Patients; 5. Vaccine and Therapeutics; 6. Other Tick-Borne Diseases and Coinfections. CDC and NIH projects align with five out of the six subcommittees topic areas with the exception of Access to Care; meanwhile DoD's activities align with two subcommittee topic areas (Disease Vectors and Surveillance and Vaccine and Therapeutics). Though FDA indicated not having an established program dedicated to tick-borne diseases, they reported some activities that align with all of the six subcommittee topic areas. These activities are carried out within existing FDA major activities.

In its survey, the Working Group also inquired about the existence of a strategic plan to address Lyme disease and other tick-borne diseases. Of the six agencies, only CDC and DoD indicated having a readily available plan. CDC and NIH report engaging in both vector and human surveillance while DoD focuses exclusively on vectors. Following the establishment of Lyme disease as a nationally notifiable condition in 1991, CDC initiated systematic tracking within 11 participating states in 1992. From 2010 to 2016, between 30,000 to 38,000 cases of Lyme disease were reported to CDC each year. However, reported cases are known to be an underestimation of diagnosed cases of Lyme disease and other tick-borne diseases.

With the exception of DoD, which tracks diagnosis of its Servicemembers, no other agency reported tracking cases or diagnosis in its survey. From October 2009 to September 2017, DoD reported that 708 active duty Servicemembers were diagnosed with Lyme disease or other tick-borne disease. Of those, 549 were stationed within the United States.

## Intramural and Extramural Activities

CDC, NIH, and DoD have managed over 1,500 past and ongoing tick-borne disease projects from fiscal year 2010 to 2018. During the same timeframe, over 750 tick-borne disease-related publications were released by four agencies: CDC-467; NIH-235; DoD-41; FDA-7.

Also during that time, approximately \$554 million have been invested in tick-borne disease related-projects, activities, and research by CDC, NIH, FDA and DoD. For example, DoD’s Tick-Borne Disease Research Program (TBDRP) was established in 2016 to support innovative and impactful research that addresses issues and gaps in tick-borne diseases. Table 3 outlines the program’s budgetary allocations during its first two years.

**Table 3. Tick-Borne Disease Research Program Funding Allocations (Department of Defense)**

|                         | 2016          | 2017          |
|-------------------------|---------------|---------------|
| Budget                  | \$4.8 million | \$4.5 million |
| Number of Awards        | 7             | 6             |
| Funding of Treatment    | 44%           | 0%            |
| Funding of Pathogenesis | 31%           | 32%           |
| Funding of Prevention   | 16%           | 48%           |
| Funding of Diagnosis    | 9%            | 20%           |

In addition, FDA invests in tick-borne disease activities within its departments. The Center for Devices and Radiological Health (CDRH) oversees approval of diagnostic assays for tick-borne diseases; the Center for Biologics Evaluation and Research (CBER) manages licenses for blood screening assays (for example, Babesia) and vaccines for tick-borne diseases; and the Center for Drug Evaluation and Research (CDER) administers the approval process for drug therapies for tick-borne diseases.



In order to understand the gaps and priorities in the tick-borne disease research, the Working Group asked the agencies to describe any unmet needs identified through their work on tick-borne diseases. Below is a list of identified priorities and gaps extracted from the survey.

- Improve early and accurate diagnosis and treatment.
- Strengthen national surveillance.
- Understand the immunological mechanism (for example, the pathogen-host interaction) of immune protection for Lyme disease and other tick-borne diseases.
- Develop new rapid and accurate lab tests.
- Develop antibiotic combination and/or therapeutic options for treating acute and persistent illness.
- Encourage the development of strategic plans for tick-borne disease federal investments.
- Dedicate funding to tick-borne diseases and evaluate related activities using performance indicators and clear metrics for success.
- Characterize how tick-borne disease affects U.S. national security, military readiness, and the health and wellness of active duty Servicemembers, Veterans, and their families.

## Appendix E: 21<sup>st</sup> 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. You can access the legislation in its entirety at [21st Century Cures Act](#).

### 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.

(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 F. 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*. The charter for the Tick-Borne Disease Working Group was approved by the Secretary of Health and Human Services on August 10, 2017. The text of the Charter is provided below.

### 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 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 \$349,440. 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 21<sup>st</sup> 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 10, 2017

Thomas E. Price  
Secretary of Health and Human Services



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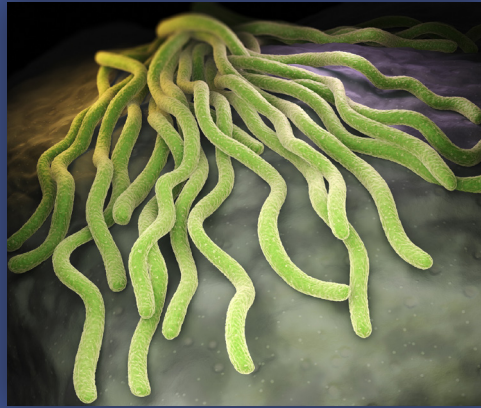
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Supported by the Department of Health and Human Services • Office of the Assistant Secretary for Health

# Tick-Borne Disease Working Group



## 2018 Report to Congress [Draft]

