



## **The Serious Consequences of Lyme and Tick-Borne Diseases**

A White Paper

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### **Overview**

Tick-borne diseases have rapidly become a serious and growing threat to public health in the United States and globally. 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 new cases each year, based on case reporting to the Centers for Diseases Control and Prevention (CDC) multiplied by an 8- to 12-fold factor to account for estimated under-reporting.<sup>1</sup> 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.<sup>2</sup>

Despite decades of research evaluating tick- and host-targeted interventions, the incidence of tick-associated diseases of humans in the world continues to rise. Scientists have identified a variety of bacterial, parasitic, and viral disease-causing agents that are transmitted by multiple tick species that bite humans. New tick-associated pathogens continue to be identified, further implicating vector ticks as an important threat to human health worldwide. *Ixodes* ticks play important roles as vectors of a variety of human disease-causing agents, with several tick species capable of carrying and transmitting multiple pathogens to humans.

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. In addition, *Ixodes* ticks have been found in approximately 50% of counties in the U.S., including many counties on the West Coast.<sup>3</sup>

At least 20 known infections can result from tick bites.

## Worldwide Implications

Lyme *borreliosis* is widely distributed, and has been reported in more than 80 countries on five continents.

**Germany** – Approximately 60,000 to 100,000 new cases of *borreliosis* are annually recorded in Germany. The prevalence of Lyme carditis is 0.3 to 4% in Europe and 1.5 to 10% in the US of all adult untreated patients with Lyme disease. This variance in disease prevalence may be due to differences in the virulence of European and northern [sic] American isolates, however mammalian model-based histopathology studies suggest that the actual rate of cardiac involvement may be much higher. A study on pediatric patients with Lyme disease found ECG changes indicative of myocardial involvement in approximately 30% of patients.<sup>4</sup>

**China** – Lyme disease was first reported in China in 1985, in a forest region in Hailin County. Human cases of *borreliosis* have been confirmed in 29 provinces/municipalities. The major endemic areas in China are forests in the Northeast and Northwest and some areas in North China. In Heilongjiang, Jilin, Liaoning, and Inner Mongolia, over 3 million people suffer tick bites annually, of those, approximately 30,000 people become infected with *borreliosis*; approximately 10% of the new cases may turn into chronic infections over 2 to 17 years without treatment. It was reported that the serological positivity of Lyme was 1.06~12.8% in the 30,000 people randomly sampled, with a mean positivity rate of 5.06% overall and 5.33% in the forests; the morbidity was 1.16~4.51% in the forests of Northeastern China, with a mean morbidity of 2.84%.<sup>5</sup>

## Lyme Projections

Tick-borne infectious diseases are a global health concern that continues to grow at an alarming rate, poses a dilemma for patients and physicians alike, and is expanding to global epidemic proportions.

In the USA by 2050, 55.7 million people (12% of the population) will have been infected with Lyme disease. In Europe by 2050, 134.9 million people (17% of the population) will have been infected with Lyme disease. Most of these infections will, unfortunately, become chronic.<sup>6</sup>

## Range and Risk of Infection

In the United States, Lyme disease is caused by *Borrelia burgdorferi sensu stricto* (*B. burgdorferi*), which is transmitted to humans by two species of *Ixodes* ticks. These ticks are prolific disease vectors because they can infect multiple hosts within a single life cycle, and they can withstand adverse environmental conditions.

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, Germany, and China, along with 80 other countries. This may be due in part to ecological changes in North America, Europe, and Asia 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.

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*. New, exotic Asian ticks such as the long-horned 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.<sup>7</sup>

## **Costs of Lyme Disease**

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.<sup>8</sup>

The estimated treatment cost for Europe is somewhere between 10.1 billion EUR and 20.1 billion EUR. If governments do not finance IV treatment with antibiotics for chronic Lyme disease, then the estimated government cost for chronic Lyme disease for 2018 is Europe 20.1 billion EUR.<sup>9</sup>

## **Pathophysiology of Tick-Borne Diseases**

Tick-borne infections can impact multiple body systems, including musculoskeletal, dermatologic, immune, orbital and ocular, cardiovascular, endocrine, and the central nervous system, and thus can manifest in unique ways in an individual patient.<sup>10</sup> The following is a list of signs and symptoms of tick-borne infections and post-treatment Lyme disease syndrome (PTLDS), but it is not inclusive of all symptoms.

**Central Nervous System:** Headaches, stiff neck, difficulty thinking/ concentrating, delayed processing time, memory loss, sleep disturbances, word searching, extreme irritability, sensory hyper-arousal (photo, sound, smell, and taste), weakness, seizures, tremors, gut abnormalities, poor balance, and stroke syndromes.

**Peripheral Nervous System–Autonomic:** Facial nerve palsy, altered sensation in trigeminal nerve, spinal or radicular pain, burning, stabbing, aching or shock sensations, numbness or tingling, muscle weakness, atrophy, fasciculations, and dizziness on standing.

**Neuropsychiatric:** Depression, anxiety, OCD, and psychosis.

**Musculoskeletal System:** Joint pain/swelling, myalgia, muscle cramps/spasms, tendonitis, and overuse syndrome.

**Cardiac:** Dyspnea, shortness of breath, non-productive cough, dizziness, syncope, palpitations, and rhythm disturbances.

**Optic:** Diplopia, blurred vision, pain in/around eyes, change in color vision, flashing lights, and peripheral waves/phantom images.

**Constitutional Symptoms:** Fatigue and fever.

**Gastrointestinal and Genito-Urinary Systems:** Diarrhea/constipation, urge incontinence and irritable bladder/interstitial cystitis.<sup>11</sup>

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 co-infection (other tick-borne pathogens), with additional pathogens such as *Anaplasma*, *Babesia*, (a malaria like parasite) 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, such as, *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.<sup>12</sup>

In addition, the following are known Lyme-related conditions.

**Lyme Carditis** – While Lyme disease most frequently affects the skin, joints, and nervous system, Lyme carditis is one of the rarer organ manifestations. However, cases with cardiac involvement can be severe and, in contrast to other *Borrelia*-associated diseases, sporadic fatal outcomes have been reported.<sup>13</sup>

Acute symptomatic cardiac involvement, which occurs in 4-10 percent of patients,<sup>14</sup> frequently results in various degrees of atrioventricular block, including complete heart block that can result in sudden death.<sup>15</sup>

A US CDC reports sudden cardiac deaths associated with Lyme carditis from Lyme disease states “patients experienced sudden cardiac death and, on postmortem examination, were found to have evidence of Lyme carditis.”<sup>16</sup>

**Lyme Neuroborreliosis** – 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. Most commonly recognized neurologic syndromes are facial nerve palsy (although other cranial nerves can be affected), meningitis, and acute painful radiculoneuritis (Bannworth’s syndrome), which can present with spine pain and dermatomal/myotomal features, [sic] The facial nerve palsy may be bilateral and accompanied by a multi-symptom complex. Patients can also present with an acute encephalitis (producing an abnormal level of consciousness, sleepiness, mood swings, psychosis, confusion, delirium [sic], or behavioral changes), acute cerebellitis (cerebellar syndrome), and acute transverse myelitis.<sup>17</sup>

There is an age specific syndrome, affecting children and adolescents, involving intracranial hypertension. However, intracranial hypertension as a manifestation of neurologic Lyme disease can occur in adults as well.<sup>18</sup> Patients present with headache and have papilledema on fundoscopic examination. Although intracranial hypertension has been associated with obesity, Lyme patients who present with this manifestation are not typically obese.

Most neurologic conditions due to late Lyme disease may be categorized as peripheral neuropathy, encephalopathy, or encephalomyelitis. Individual presentations of late neurologic disease are often complex and may include cranial neuritis (not exclusive to CN VII, any of the cranial nerves may be involved), motor and sensory neuropathies, upper motor neuron weakness or amyotrophic lateral sclerosis (ALS)-like disorders, multiple sclerosis (MS)-like disorders, autonomic dysfunction, movement disorders, cerebellar syndromes, seizures, neuropsychiatric disease, and dementia.

The most common manifestation of neurologic involvement in late Lyme disease is cognitive impairment, which in more severe cases is categorized as encephalopathy. The cognitive impairment is typically subtle to mild. Dementia, however, can be a rare manifestation of neurologic Lyme disease.<sup>19</sup>

CDC surveillance case data demonstrates that 10-15% of Lyme disease patients develop neurologic Lyme disease. However, the surveillance case data may not capture some clinical cases because the surveillance case definition requires patients to be positive on two-tier testing; patients with neurologic disease may not meet this laboratory criterion.<sup>20</sup> Although neurologic manifestations of Lyme disease are not rare, the diagnosis can elude clinicians.<sup>21</sup>

Lymphocytic meningoradiculitis, known as Garin-Bujadoux-Bannwarth syndrome, is a well-recognized complication of Lyme disease. Lymphocytic meningoradiculitis is a common form of *neuroborreliosis* in Europe.<sup>22</sup>

**Neuropsychiatric Manifestations** – Neuropsychiatric symptoms may emerge at various stages of Lyme disease. Neuropsychiatric symptoms include emotional, behavioral, sensory, and cognitive dysfunction.

Studies in adults and children suggest that depressive symptoms are not elevated in patients who present with early erythema migrans [sic]. If Lyme disease is not detected until later in infection, however, mood disorders are common.

Various well-documented case reports document that psychiatric symptoms in rare cases may be the predominant feature of *B. burgdorferi* infection, such as obsessive-compulsive disorder (OCD), mania, Tourette's Syndrome, and panic/depersonalization. In each of these cases, psychiatric treatment was initially less effective than anticipated but antibiotic therapy led to marked improvement or resolution, highlighting the importance of cerebrospinal fluid studies in atypical neuropsychiatric cases.<sup>23</sup>

Cross-sectional studies of persistently symptomatic antibiotic-treated Lyme disease reveal that irritability and depressive symptoms are common. In a study of adult patients with chronic neurologic Lyme disease (half of whom had had early antibiotic treatment), extreme irritability was noted in 26% and depression in 37%. In a large study conducted out of an academic center's rheumatology clinic, patients with persistent symptoms after well-documented Lyme disease had a nine-fold greater rate of current depression than patients whose Lyme-related symptoms had resolved (45.2% vs. 5%).<sup>24</sup> In a recent report of patients with post-treatment Lyme disease, suicidal thoughts were reported by one in five patients, largely restricted to those who had concurrent depression; while this rate was not greater than in a comparison group of those with HIV infection, it was 4 times greater than in the non-patient control group. Because active suicidal intent was reported by 12.5% of those with suicidal thoughts (2 of 16), this report highlights the importance of screening for depression and suicidality in patients with chronic symptoms, a finding consistent with an earlier case series.<sup>25</sup>

**Pathophysiologic Mechanisms** – The pathophysiology of neuropsychiatric symptoms in Lyme disease is multi-factorial, involving both physical and psychologic processes. The physical processes may reflect the inflammatory response to active infection, damage from the prior inflammatory reaction, or possibly molecular mimicry induced by the infection leading to cross-reactive antibodies which target neural tissue. The intrapsychic, interpersonal, and societal stressors that accompany Lyme disease may lead to psychological symptoms, particularly alterations in mood such as depression and anxiety. These stressors include persistent pain, cognitive impairment, severe fatigue, financial and job losses, functional disability, interpersonal isolation, invalidation by medical professionals, altered sense of identity due to inability to live up to one’s own expectations as a caregiver or financially self-supporting adult, or sense of a foreshortened future.<sup>26</sup>

**Vision Impairment** – Ophthalmic manifestations of tick-borne diseases are increasing in the United States, according to a review published recently in *Current Opinion in Ophthalmology*. Delays in diagnosis may result in vision impairment and even blindness.<sup>27</sup>

Lyme disease in humans produces a multi-systemic, multi-staged illness, and while disease manifestations have been well characterized, host-pathogen interactions and the resultant pathophysiology are poorly understood. The number and severity of disease manifestations vary greatly from patient to patient suggesting that host determinants play a role. Tissue tropism (bacterial preference for certain tissues) is notable, but factors driving this selectiveness are unknown. Many of the most challenging symptoms and signs that patients contend with are neurological in nature, yet how *B. burgdorferi* interacts with the nervous system is uncertain. Possibilities include 1) the release of lipoproteins into the circulation that cross the blood brain barrier and act via inflammation or direct effects on neural tissue, 2) pro-inflammatory cytokines, and 3) the formation of autoantibodies and/or cross-reactive antibodies.

The pathophysiology underlying ongoing symptoms and signs in patients previously treated for Lyme disease is not understood. Potential mechanisms include immune dysfunction, tissue injury, untreated co-infections, and persistent *B. burgdorferi* infection; these mechanisms are not mutually exclusive.

Given the uncertainty regarding human pathophysiology in Lyme disease, continued research is required as an increased understanding of the infection should translate to improved patient care.<sup>28</sup>

## Millions Remain Chronically Ill

While most Lyme disease patients who are diagnosed and treated early can recover, 10% to 20% of patients suffer from persistent symptoms, which for some are chronic and disabling. Using a research definition of and data on 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 US patients with a clinical diagnosis of chronic Lyme disease may be larger, but is unknown.

Due to unreliable tests and lack of awareness, Lyme patients are often misdiagnosed with other diseases, such as rheumatoid arthritis, MS, ALS, autism, and Alzheimer's disease.

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 co-infections such as *Babesia*, a malaria-like parasite, *bartonella*, or *Anaplasma*. Moreover, many patients experience chronic and recurring symptoms after antibiotic treatment for Lyme disease, other tick-borne diseases, and co-infections. This chronic illness is poorly understood and often results in significant deterioration in the quality of life of patients and their families.

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 co-infecting pathogens in order to design and test new therapies and, ultimately, improve outcomes and care for patients with ongoing symptoms.<sup>29</sup>

## Major Challenges and Issues

The serologic enzyme-linked immunosorbent assay (ELISA) test detects antibodies against *B. burgdorferi* and is currently the only type of laboratory test cleared by the FDA and recommended by the 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 co-infections.<sup>30</sup>

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.<sup>31</sup>

Lyme disease is the most commonly reported tick-borne infection in the United States, however a single tick can transmit a number of pathogens, referred to as co-infections, during one bite such as *anaplasmosis*, *ehrlichiosis*, *babesiosis*, *rickettsioses*, Powassan virus disease, Bourbon virus disease, and *Borrelia miyamotoi* disease and many others. This can confound diagnosis and treatment. Most health care professionals have received little or no training on diagnosing or interpretation of testing for tick-borne diseases. There is a lag time between the onset of symptoms and when tests can measure antibodies. Lyme disease antibody tests are inaccurate during the first few weeks of infection, when treatment is most effective. As a result, most patients miss the window of early diagnosis and treatment, allowing their condition to become increasingly more challenging if not impossible to treat. Often they receive a false negative test and go untreated or misdiagnosed. Some of the *Borrelia* species are not detected by standard two-tiered testing for Lyme disease and may persist following CDC guideline therapies and may result in increased morbidity and mortality.

## US Federal Funding for Lyme

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 about \$53,000 and \$14,000 respectively, per new case of HIV/ AIDS, and \$82,000 and \$26,000 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.<sup>32</sup>

## US Federal Funding for Selected Infectious Diseases<sup>33</sup>

Disease	US 2016 Cases <sup>a</sup>	NIH 2017 Appropriations	CDC 2017 Appropriations
Hepatitis C	3K	\$107M	\$34M
HIV/AIDS	39K	\$3B	\$787M
Influenza	9.2 to 35.6M <sup>b</sup>	\$263M	\$187M
Vector-borne diseases <sup>c</sup>	60K	\$46M	\$26M
Lyme disease	36K 291– 437K <sup>d</sup>	\$28M	\$11M

- a. CDC has not published statistics for 2017.
- b. CDC estimates for seasonal influenza from low to high over seasons.
- c. Vector-borne diseases include malaria, Zika, dengue fever, West Nile Virus, etc. and do not include Lyme disease, yet most common.
- d. Lyme disease estimates are based on case reporting to the CDC and multiplied for an 8- to 12-fold factor to account for estimated underreporting.

## The Need for Targeted Interventions

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 their associated pathogens, 3) further study of methods aimed at blocking transmission of tick-borne pathogens to humans and animals, and 4) adequately validating that these methods can effectively reduce the incidence of tick-borne illnesses

using prospective studies that measure both acarologic and human outcomes.<sup>34</sup>

**Non-Antimicrobial Drugs for Late-Lyme Arthritis and PTLDS** – As John Aucott, MD, Director, Johns Hopkins Lyme Disease Clinical Research Center, has reported, several non-antimicrobial drugs are used off label in two categories of patients—those with antibiotic-refractory late-Lyme arthritis and others with PTLDS. Medications used to treat antibiotic-refractory late-Lyme arthritis include hydroxychloroquine, methotrexate, and biologicals, whereas a plethora of medications are used to treat pain, fatigue, and cognitive symptoms in patients with PTLDS.

There are several underlying reasons for the wide range of approaches to care for patients who have PTLDS. Key reasons include patient and physician uncertainty as to the cause of PTLDS symptoms with attendant medical ambiguity as to how to respond. Patients with PTLDS show evidence of anatomic neurologic damage with deficits in cognitive processing that can be measured during neurocognitive testing. Availability of FDA/EMA-approved drugs to treat PTLDS might help address some of these issues.

**Opportunities for Development of New Therapeutics for Lyme Disease** – An opportunity for development addresses the role that bacterial persistence might play in Lyme arthritis and PTLDS. Bacterial persistence is a widespread phenomenon that was first reported in the medical literature in 1942. In cases of bacterial persistence, antibiotic-tolerant cells, which are referred to as “persister cells,” are present in small amounts despite antimicrobial treatment, and they are less susceptible to antibiotics than normal antibiotic-sensitive cells.

**Antimicrobial and Non-Antimicrobial Therapeutics for Lyme Disease** – A deeper understanding of what causes PTLDS is needed to select appropriate treatment for patients who continue to experience clinical signs and symptoms following treatment with currently available antibiotics. The causes may differ among patients. Nevertheless, there are sub-populations of patients who develop PTLDS after undergoing recommended treatment. To date, none of the currently available non-antimicrobial therapeutics have label indications for relief of pain, fatigue, and cognitive symptoms resulting from infection with *B. burgdorferi* or for treatment of the infection itself, and efficacy studies for such therapeutics are very limited.

Dr. Aucott’s data documents how patients with PTLDS feel and function. Clearly, more needs to be done to address the signs and symptoms of PTLDS, which usually differ from the clinical manifestations (such as rash, neuropathy, or joint swelling) typically associated with untreated infection. Ideally, the approach would be based upon a clearer understanding of the genesis of PTLDS symptoms in each patient. Causes to consider include effects of a protracted host immune response, other causes of autoimmunity or cross-reactivity, collateral effects of prior antibiotic treatments, and systemic responses to bacterial persistence. With

direction provided by increased scientific evaluation of the pathogenesis of illness, evidence-based therapeutics can be more effectively developed. Emphasis on understanding the causes of disease and improving symptom management represent opportunities to move beyond some of the ongoing controversy regarding strategies for treatment of PTLDS.<sup>35</sup>

## **A Comprehensive Response**

As is known from the literature and the clinical experience of doctors who diagnose and treat patients with Lyme disease, patients can have many different disease manifestations. Diagnosis and treatment is made more difficult because the pathogen itself can only rarely be detected in the blood, early diagnosis does not always occur, and pathogen eradication cannot be proven following treatment. There are many gaps in the scientific understanding of the pathophysiology of Lyme disease. In considering these gaps, they have categorized them as either related to disease manifestations in humans and gaps regarding what is known about the pathogen(s).<sup>36</sup>

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 world, 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.<sup>37</sup>

A strategic approach to public/private partnerships and collaborations, so that tick-borne diseases are a global priority, will better harness the power, resources, commitment, and innovation across all sectors—industry, academia, and nonprofit organizations, as well as governments.

## **Innovation Required**

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 global priority response with 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.<sup>38</sup>

## Summary

The continued spread of ticks, the discovery of new tick-borne pathogens, and the spreading outbreak of human disease is a near certainty. A global epidemic poses a dilemma for patients and physicians alike. Current CDC diagnostics are unreliable and guidelines are dated and fail to restore quality of life, subjecting patients to personal suffering, deterioration with loss of function and income, and even death.

Lyme disease...

- is a US public health epidemic and spreading at an alarming rate globally, yet the public and the medical community is [sic] largely unaware of the risks.
- is the fastest growing, infectious disease in the US, costing the US health care system billions, yet R&D is significantly underfunded.
- has over 300,000 new cases reported each year in the US alone, which is six times more than HIV, yet the National Institute of Health Lyme budget is less than 1% of that of HIV.
- is 20 times more common than Hepatitis C.
- does not have a reliable diagnostic currently available. The standard tests miss up to 60% of cases. Present treatments are failing patients—leaving them debilitated.
- is caused by a spirochete bacterium, similar to syphilis and typically transmitted by the bite of an infected tick.
- can cause developmental consequences for children who contracted the bacterium from their mothers in utero.
- if not diagnosed and treated promptly, may progress to a debilitating stage becoming difficult, or impossible to treat and can be potentially fatal. There is no curable treatment currently available.
- patients are often misdiagnosed with other diseases, such as, rheumatoid arthritis, MS, ALS, autism and alzheimer's due to unreliable diagnostics and lack of awareness.<sup>39</sup>

Furthermore...

- The absence of a reliable screening leaves our blood banks at risk.
- Delays in Lyme disease diagnosis may result in vision impairment and even blindness.
- Millions remain chronically afflicted, causing them to not only suffer from lost income but to even be penalized with exorbitant out-of-pocket medical costs due to the lack of health insurance coverage for Lyme disease.
- The persistent neurologic, cognitive, and musculoskeletal symptoms that can accompany Lyme disease pose a major burden to patients and their families, and yet how the tick-borne infection causes these symptoms is not well understood. The mechanisms and thus the solutions are complex.
- Without deep understanding of these fundamental aspects of Lyme disease and its effects on the systems of the body, the translation of new knowledge to immediate clinical care strategies has lagged far behind other health conditions affecting such large patient populations in the world.<sup>40</sup>

### **Recommendations:**

- Improve early and accurate diagnosis and treatment.
- Strengthen global surveillance.
- Understand the immunological mechanism 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.
- Dedicate funding to tick-borne diseases and evaluate related activities using performance indicators and clear metrics for success.

## Lyme Disease Case Studies

### Neil Spector, MD

Lyme Disease Survivor and Patient Advocate,  
Associate Professor of Medicine Duke University School of Medicine Durham,  
North Carolina

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 for Lyme disease. He first began to experience a bizarre constellation of symptoms in 1993, which including cardiac arrhythmias and profound fatigue. Dr. Spector states, "I went from running 10 miles a day, six days a week to barely being able to walk 10 yards without feeling exhausted." Doctors couldn't find anything wrong with him. He added, "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 antibiotics for him 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, his symptoms were dismissed 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. This manifestation of Lyme disease brought Dr. Spector to the brink of death, and he had to have a heart transplant to save his life.

## **Julia Bruzzese and Family**

Julia Bruzzese was a lively nine-year old when she was bitten by a tick and contracted Lyme disease and associated co-infections. Although she had a bulls-eye rash and was taken to a pediatrician after the tick bite, and for many subsequent sick visits, Julia went undiagnosed for more than two years. After Julia received numerous, extensive serological workups for every possible diagnosis, and despite the fact that she was suffering from early stages 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 younger 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 of the 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. However, because treatment was delayed for so long, Julia still suffers from the chronic effects of Lyme and remains in a wheelchair.

## Colonel Nicole Malachowski

USAF, Ret. Career officer, leader, fighter pilot  
First woman pilot, USAF Air Demonstration Squadron (“Thunderbirds”)

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

In the following four years, she saw more than twenty doctors across eight specialties. Her neurological symptoms continued to worsen, but none of the doctors knew why and some suggested it was psychosomatic. She was suffering from intensifying fatigue, joint and muscle pain, vestibular issues, ocular manifestations, sensory problems, cognitive dysfunction, etc. She was misdiagnosed with everything from possible multiple sclerosis, to autoimmune disease, to fibromyalgia. Eventually she could no longer work in the military as a fighter pilot, and the military began steps to medically retire her—she was permanently, medically retired from the career she loved at the age of 43, after having served in the military for more than 21 years.

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

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

Because her illness went undiagnosed for so long, she does not know all the treatment she will need and how long her recovery will last. She went from someone who could not get out of bed to someone who can take her seven-year-old twins to their soccer games. While she has not recovered completely, she now has a life worth living.<sup>41</sup>

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