3rd Report

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

Tick-Borne Disease Working Group

2022 Report to Congress

Table of Contents

Contributions

U.S. Department of Health & Human Services

James (Jim) Berger, MS, MT (ASCP), SBB
(Designated Federal Officer)

B. Kaye Hayes, MPA
(Alternate Designated Federal Officer)

Tick-Borne Disease Working Group Members

Holiday Goodreau (Co-Chair)

Linden Hu, MD (Co-Chair)

Charles Benjamin (Ben) Beard, PhD

CAPT Rebecca Bunnell, MPAS, PA-C

Dennis Dixon, PhD

Monica E. Embers, PhD

Elizabeth Maloney, MD

Robert J. Miller, PhD

CDR Todd Myers, PhD, HCLD (ABB), MB (ASCP)

Jennifer Platt, DrPH

Sunil K. Sood, MD

Kirby C. Stafford III, PhD

Leith Jason States, MD, MPH (FMF)

Gabriella Zollner (Romero), PhD

For additional information, visit the Tick-Borne Disease Working Group website.

Figures

Tables and Text Boxes

Executive Summary

In this third and final report of the Tick-Borne Disease Working Group, the committee applauds the progress that has been made during the past six years but recognizes the challenges that remain. The Working Group identified possible paths toward achieving its vision of "a nation free of tick-borne diseases where new infections are prevented and patients have access to affordable care that restores health."

This report is divided into chapters that are similar to those of the prior Working Group reports, including Introduction and Background; Public Comments; Access to Care and Education; Changing Dynamics of Tick Ecology; Personal Protection, and Control; Clinical Presentation and Pathogenesis; Diagnostics; Disease Prevention and Treatment; Conclusion and Looking Forward. These chapters, written by Working Group members, were informed by the work of expert subcommittees that explored each topic and identified priority issues for Working Group consideration. The priority issues guided the formulation of the Working Group's recommendations to Congress for the federal response to combatting tick-borne diseases and associated illnesses.

Although the substance of each recommendation centers on its associated topic area, several common themes emerged and are shared across this report. First, multiple subcommittees highlighted that federally organized programs have been the best means for making progress in their topic areas—underscoring the breadth and diversity of the diseases caused by ticks. They identified key areas requiring additional action, including disease and tick surveillance, biorepositories for specimens from patients with tick-borne diseases that would speed discovery, and national databases that collate information from multiple sources. These areas extend beyond the scope of individual researchers, companies, or academic institutions and would benefit from the capacities of federal government agencies, such as the National Institutes of Health and the Centers for Disease Control and Prevention, to organize them. The commitment of national-level resources in these areas would accelerate recognition of new threats, development of new diagnostics and treatments, and identification of the pathogenesis of disease.

Second, several subcommittees cited increased government intervention in the development of diagnostics and treatment protocols as detrimental to transforming the tick-borne disease landscape. The subcommittee members believed that progress has been impeded by a heavy regulatory burden and low likelihood of profitability, which discourage the private-sector investments needed to catalyze the entry of new products into the market. This type of market investment is not a novel approach to solving complex public health issues, as evidenced by the mission of federal entities such the Biomedical Advanced Research and Development Authority (BARDA) to "develop and procure needed medical countermeasures, including vaccines, therapeutics, diagnostics, and non-pharmaceutical countermeasures, against a broad array of public health threats." In fact, this approach to accelerating high-risk, high-reward research

to drive biomedical and health breakthroughs has been expanded by the U.S. Department of Health and Human Services with the establishment of the Advanced Research Project Agency for Health (ARPA-H) in 2022. The deficiencies identified in the tick-borne disease diagnostics and therapeutics discovery pipelines align with the defined mission of BARDA and the future role of ARPA-H. Development of a tick-borne disease portfolio in either entity would likely improve coordination across agencies and accelerate progress toward improving patient care.

Third, a new major theme identified by multiple subcommittees is the prioritization of health equity for sufferers of tick-borne diseases and associated illnesses. Recent advances in the care of at-risk patients include improved access to telemedicine in areas where health care providers lack expertise in tick-borne diseases and associated illnesses; better understanding of the clinical presentation of tick-borne diseases, particularly in populations that are commonly under-evaluated such as prisoners, individuals in psychiatric facilities, and migrant workers; establishment of safety standards for individuals in high-risk occupations; and labeling of food, medical, and commercial products to protect patients with Alpha-gal Syndrome.

Fourth and finally, within each area, the Working Group and its subcommittees identified understudied areas that would benefit from targeted funding opportunities. Many of these areas were identified in prior Working Group reports and are highlighted here again as lacking significant progress. These areas include development of tick control and preventative agents against tick bites; improved diagnostics for multiple diseases; vaccines; treatments for tick-borne viruses and persistent symptoms of Lyme disease; and additional studies of central nervous system and psychiatric manifestations

of tick-borne illnesses, effects on pregnancy, and development of post-tick bite allergies to alpha galactosidase.

Although much has been accomplished since the first Report to Congress in 2018, the Working Group recognizes that much remains to be done. This report highlights the important goals still to be accomplished and the way forward to reduce the impact of tick-borne diseases in the United States.

Recommendations at a Glance

Chapter 3: Access to Care and Education

Recommendation 3.1: Provide funding for the U.S. Department of Health and Human Services to sponsor the National Academy of Medicine (NAM) within the National Academies of Sciences, Engineering, and Medicine to conduct an objective, comprehensive review of the basic science and clinical evidence for diagnosis and treatment of Lyme disease, with emphasis on acute and Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD). The purpose for conducting an objective review would be to establish what is definitely known, what is partially understood, and what remains unknown about Lyme disease. The review mechanism shall be transparent and include public stakeholders and patient representatives, experts in trial design and execution, as well as a diversity of experts who represent the full spectrum of scientific perspectives on Lyme disease. The expert panel will produce a comprehensive public report, which will be used to inform federal and state initiatives.

Recommendation 3.2: Upon activation of Recommendation 8.1 of the Tick-Borne Disease Working Group 2022 Report to Congress outlining implementation of Working Group priorities, the first recommendations to be discussed for updates and public input are Recommendations 7.1 and 7.2 from the Tick-Borne Disease Working Group 2020 Report to Congress that address educational materials and web content. Emphasis should be placed on receiving input via meaningful engagement with stakeholders on how these recommendations have been implemented to date across HHS operating divisions and how well they reflect the current state of the science.

Recommendation 3.3: Fund and support continued and ongoing modification of the federal government websites, starting with the CDC and NIH websites, as well as educational materials and seminars for clinicians, the public, and public health departments to reflect the current state of the science related to Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD), which is limited, emerging, and unsettled, and to acknowledge that there are divergent views on diagnosis and treatment of patients with PLD/CLD.

Recommendation 3.4: Provide the HHS Secretary with discretionary authority to maintain telehealth flexibilities independent of Public Health Emergency declaration for patients with tick-associated illnesses in order to ensure access, parity, and equity for those receiving in-person and telehealth services.

Recommendation 3.5: Fund, support, and encourage community-based participatory research programs for Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD) and complex presentations of late Lyme disease and other tick bite-associated illnesses. This includes the development and growth of community research capacity to accelerate the fundamental knowledge base using "big data" registries, data-sharing platforms, specimen and tissue sample repositories, and genomic and precision medicine approaches that reflect the underlying heterogeneous nature of tick-borne diseases and associated illnesses.

Chapter 4: Changing Dynamics of Tick Ecology, Personal Protection, and Control

Recommendation 4.1: Increase funding for research on tick ecology towards more effective tick and tick-borne disease surveillance and tick control. Tick ecology is an important part of the One Health concept that also includes people and companion animals.

Recommendation 4.2: Increase funding to develop, evaluate, and deploy tick bite prevention and tick control approaches and strategies. Minimize roadblocks and streamline the regulatory process for getting new tick bite prevention and tick control products to market.

Recommendation 4.3: Increase adoption and expand knowledge of tick bite prevention and tick control methods across all affected groups, including implementation of occupational standards for employees at high risk of tick-associated illnesses.

Chapter 5: Clinical Presentation and Pathogenesis

Recommendation 5.1: Support additional research on the mechanisms of pathogenesis of tick-borne disease, with a particular focus on central nervous system infection (including neuropsychiatric illness and neuropathic injury), persistent symptoms, allergy (Alpha-gal Syndrome), immunity, autoimmunity, pregnancy, and adverse fetal outcomes.

Recommendation 5.2: Provide funding to support research investigating the prevalence of undetected tick-borne illness among subgroups of the population who may have multi-systemic chronic conditions (e.g., mental illness, musculoskeletal diseases, etc.) and who have been inadequately medically evaluated, including individuals in psychiatric facilities, prisons, homeless shelters, and other populations experiencing health disparities or disabilities.

Recommendation 5.3: Require labeling of foods, products, beverages (including alcohol), cosmetics, and pharmaceuticals that contain non-primate mammalian ingredients (active or inactive) and update the FDA's Food Safety Modernization Act to incorporate Alpha-gal Syndrome (AGS) awareness training into the FDA's "Retail Food Industry/Regulatory Assistance and Training" Program.

Recommendation 5.4: Provide funding for studies, particularly prospective studies, that evaluate clinical similarities, mechanisms of pathogenesis, and common etiologies for long COVID and other infection-associated chronic illnesses, with tick-associated chronic illness and/or persistent symptoms associated with tick-borne diseases.

Recommendation 5.5: Develop and maintain comprehensive biospecimen repositories (e.g., whole blood, sera, cerebrospinal fluid, maternal and fetal tissues and fluids, and autopsy specimens) for use in developing and/or improving diagnostic assays, both direct and indirect, and for research into transmission and pathogenesis, for broad applications including early diagnosis, distinction of current versus past infection, and for use in pregnancy and fetal outcome applications.

Chapter 6: Diagnostics

Recommendation 6.1: Convene a panel of stakeholders and experts in tick-borne disease diagnostics, including but not limited to researchers, government, investors, small businesses, large clinical labs, patient advocates, and diagnostics companies, with the goal of promoting the evaluation and development of current and promising new diagnostic approaches.

Recommendation 6.2: Recommend increases in federal funding (CDC or NIH) to: (1) build a national biorepository of human clinical specimens for tick-borne disease supported by a national network of qualified labs and physician clinics; and (2) build a clinical and translational research program involving a network of clinical and academic centers.

Recommendation 6.3: Provide federal support for tick-borne-disease diagnostics through an innovation pipeline with direct Congressional appropriations for a tick-borne-disease innovation accelerator and system that provides targeted funding opportunities, use authorization, lab-to-market commercialization, and implementation via relevant federal agencies.

Chapter 7: Disease Prevention and Treatment

Recommendation 7.1: Improve the quality, timeliness, and completeness of surveillance and reporting of tick-borne diseases nationwide. The resulting information should be used to educate health care providers and the public to prevent, diagnose, and treat tick-borne diseases.

Recommendation 7.2: Increase funding to develop multi-pathogen vaccines, "anti-tick" vaccines, and new prevention strategies to provide broad protection against different tick-borne pathogens. Research on stand-alone Lyme disease vaccines should look for alternatives to human OspA-based vaccine approaches.

Recommendation 7.3: Accelerate discovery, preclinical and clinical development of effective treatments for tick-borne diseases. Increase funding for research into understudied areas of treatment for tick-borne diseases, including but not limited to pediatric neuropsychiatric illnesses, pregnancy outcomes in infected women, and in all age groups, persistent post-treatment symptoms with emphasis on Lyme disease.

Chapter 8: Conclusion and Looking Forward

Recommendation 8.1: Request that following sunset of the Tick-Borne Disease Working Group, HHS's Office of the Assistant Secretary for Health (OASH) convene regular virtual public co-creation or collaboration workshops and technical consultations, in concert with relevant HHS operating divisions (CDC, FDA, NIH, and CMS) and with other relevant federal departments to share updates and receive input on progress made towards implementing federal advisory committee (FAC) recommendations from the three reports to Congress. The recommendations should be tracked back to the Goals, Strategies, and Objectives of the anticipated national public health strategy for the prevention and control of vector-borne diseases in humans, of which HHS/OASH is currently leading the development, to ensure progress is made on recommendations, as resources allow. Through these regularly convened public engagement sessions, public input should be collected and an open dialogue should be supported to ensure continued, meaningful engagement with the tickborne disease community (including patients, advocates, scientists, clinicians, and educators).

Chapter 1
Introduction and Background

Current State of Tick-Borne Diseases in the United States

Each year in the United States, hundreds of thousands of people fall ill from the bite of a tick. Diseases such as Lyme disease, ehrlichiosis, and anaplasmosis cause significant morbidity, and each year deaths are officially reported, primarily from Rocky Mountain spotted fever and Powassan virus encephalitis. Reported cases of tick-borne diseases are increasing in the United States. In 2019, the most recent year for which national surveillance data are available, more than 50,000 cases were reported for the tick-borne

diseases with the five highest incidence (CDC, 2021g) (Figure 1). Furthermore, reported cases significantly under-represent the total numbers of infections. For example, with Lyme disease, recent studies based on insurance claims data estimate that more than 476,000 cases are diagnosed and treated each year in the United States (Kugeler et al., 2021), compared to a previous similarly derived estimate of around 300,000 cases (Hinckley et al., 2014; Nelson et al., 2015). Under-reporting rates of similar magnitudes have been documented for anaplasmosis and ehrlichiosis (Dixon et al., 2021).
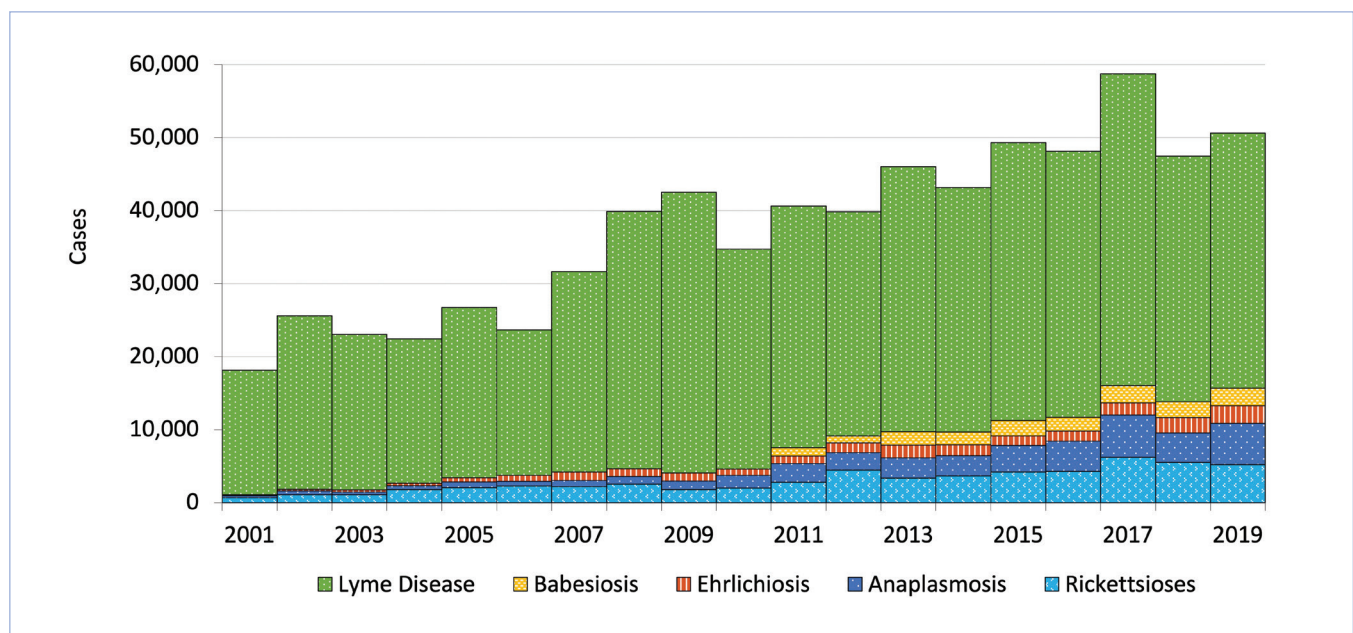
Figure 1. Reported cases of the most common tick-borne diseases in the United States.
Source: CDC, 2021g.

During the past 20 years, reported cases of tick-borne diseases have more than doubled, and during the past 25 years, the number of counties where the key vector species—the blacklegged tick *Ixodes scapularis*—is now established has also more than doubled (Beard et al., 2019). The lone star tick (*Amblyomma americanum*), once limited largely to the southern United States, can now be found in New England. Corresponding with the geographic expansion of this tick species, increasingly more cases of Alpha-gal (galactose-α-1,3-galactose) Syndrome are being documented (Binder et al., 2021).
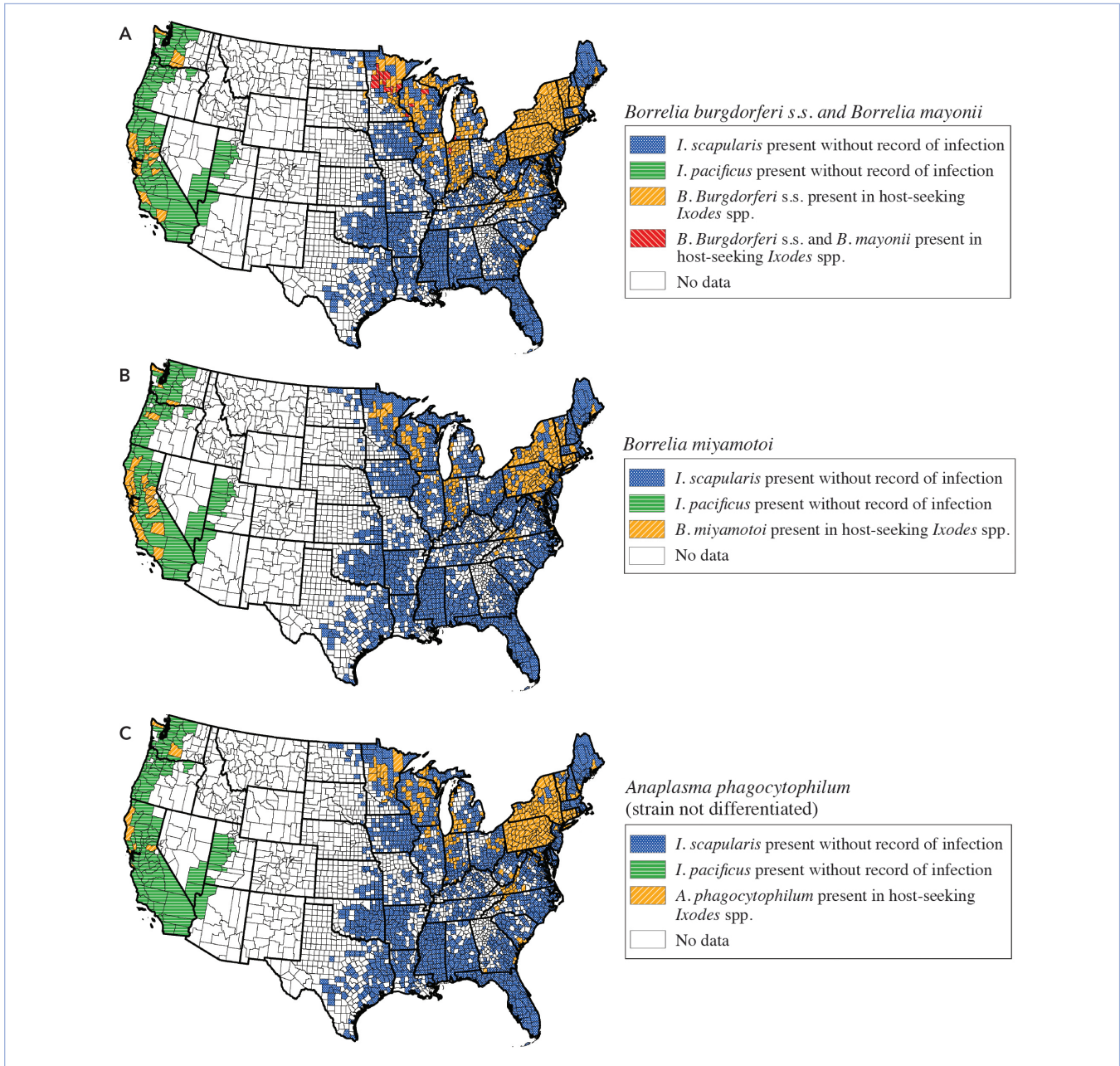
Figure 2A. County-level distribution of pathogens in ticks.

(A) *B. burgdorferi* s.s. and *B. mayonii*, (B) *B. miyamotoi*, and (C) *A. phagocytophilum* (strain not differentiated), in host-seeking *I. scapularis* (eastern United States) or *I. pacificus* (western United States), relative to the previously reported distribution of these vector species. Ticks were considered present in a county if at least one tick was recorded. Counties where ticks have been reported without records of infection may be reported as such either if ticks were not tested or if the pathogen was not detected in tested samples.

Source: CDC, 2021g. Data are continuously updated and available on CDC's Tick Surveillance page.

Finally, as tick populations expand and expose greater numbers of people to the bites of infected ticks, new tick-borne pathogens are being recognized as the cause of illness in humans. These causes include a range of bacterial and viral pathogens, such as Heartland virus, which has resulted in severe human infections including death, across the central region of the United States (Brault et al., 2018) (Figure 2A and Figure 2B). Tick-borne diseases and associated illnesses represent a public health emergency for which greater government investments for surveillance and for research into more effective tools for prevention, control, and treatment are urgently needed.
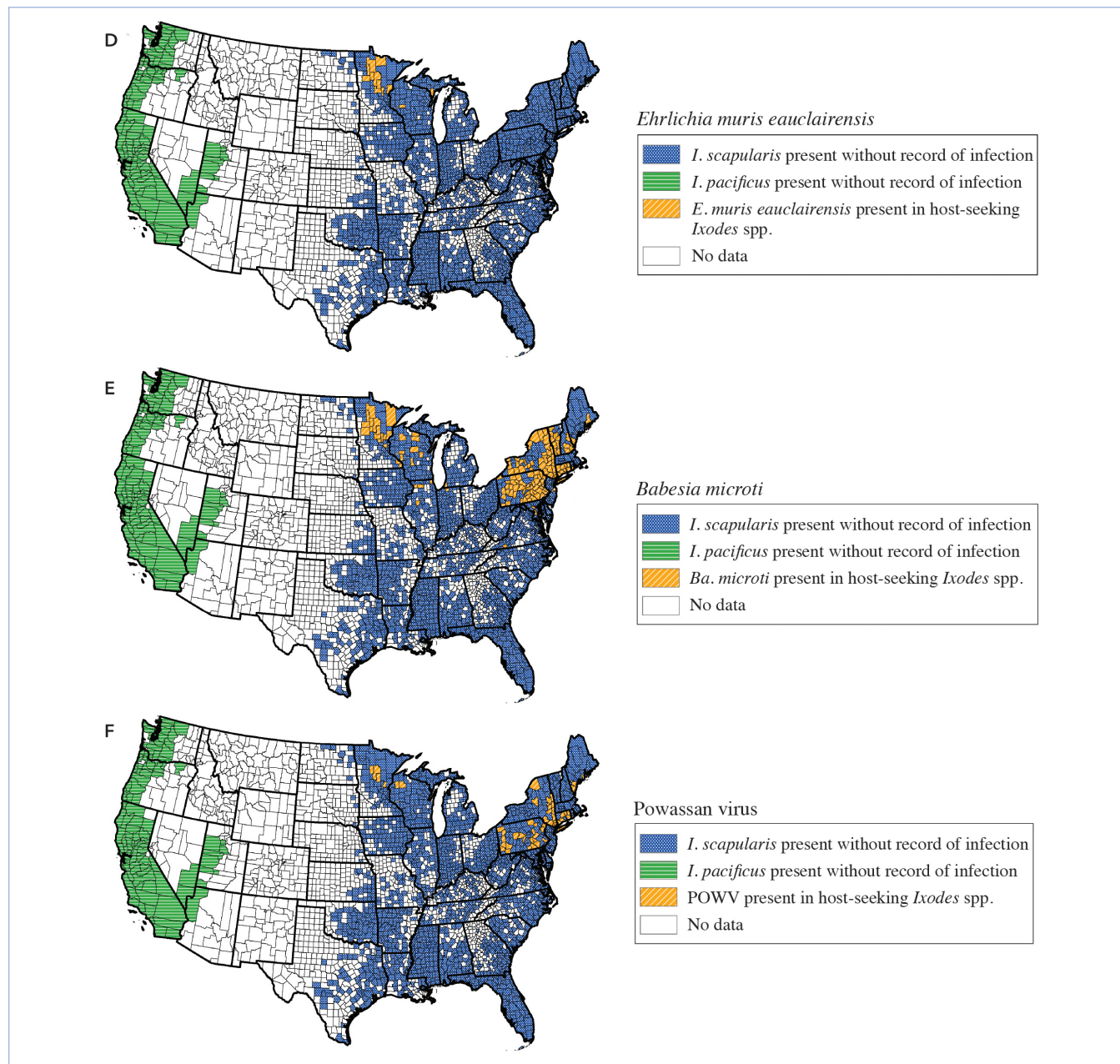
Figure 2B. County-level distribution of pathogens in ticks.

Reported county-level distribution of (D) *Ehrlichia muris eauclairensis*, (E) *Babesia microti*, and (F) Powassan virus in host-seeking *Ixodes scapularis* (eastern United States) or *Ixodes pacificus* (western United States), relative to the previously reported distribution of these vector species. Ticks were considered present in a county if at least one tick was recorded. Counties where ticks have been reported without records of infection may be reported as such either if ticks were not tested or if the pathogen was not detected in tested samples.

Source: CDC, 2021g. Data are continuously updated and available on CDC's Tick Surveillance page.

9

Sen. Kay Hagan

The late U.S. Senator Kay Hagan of North Carolina was a noted politician, banking executive, and mother. Hagan served in the U.S. Senate between 2009 and 2015 and previously served for more than a decade in the North Carolina State Senate. Her passing at age 66 after a three-year battle with encephalitis caused by Powassan virus disease raised awareness of this rare virus and the consequence of tick-borne disease. Her passing inspired the passage of the Kay Hagan TICK Act, which authorized the continuation of CDC's Regional Centers for Excellence in Vector-Borne Diseases for another five years, authorized additional funding to CDC to support the Epidemiology and Laboratory Capacity cooperative agreement, and authorized HHS to develop and implement a national strategy to address vector-borne diseases, including tick-borne diseases.

Federal Response to Prior Working Group Recommendations

Since its inception in 2016, the Tick-Borne Disease Working Group has collected input from an array of experts and stakeholders with the goals of outlining the status of tick-borne disease research and activities in the United States and identifying areas of need. The Working Group's first two Reports to Congress, published in 2018 and 2020, contained a total of 55 recommendations. These recommendations prompted or supported several important federal actions, beginning with the passage of the Kay Hagan Tick Act in 2019 (S.1657, 116th Congress, 2019-2020), which authorized the appropriation of $10 million annually for fiscal years (FYs) 2021 through 2026. From FY 2018 to FY 2021, funding to the National Institutes of Health (NIH) for tick-borne disease activities increased by $36.4 million, the Centers for Disease Control and Prevention (CDC) by $9.3 million, and the Department of Defense by $3.1 million (OIDP, 2022).

Other recent federal efforts include the publication of a Strategic Plan for Tick-Borne Disease Research by NIH (2019) and the launch of the U.S. Department of Health and Human Services (HHS) LymeX Innovation Accelerator, a public-private partnership with the Steven & Alexandra Cohen Foundation. In addition, CDC initiated its National Tick Surveillance Program and worked cooperatively with five federal departments and the Environmental Protection Agency to develop the National Public Health Framework for the Prevention and Control of Vector-Borne Diseases in Humans (2020). CDC also published a variety of resources related to tick-borne diseases and associated illnesses, including continuing education modules for providers and educational materials for both providers and the public. (See *The 2022 National Inventory of Tick-Borne Diseases and Associated Illnesses* for a more detailed accounting of federal funding and activities for tick-borne diseases and associated illnesses since FY 2018.)

The Working Group acknowledges the significance of these activities and urges continued investment in their perpetuation. However, many recommendations have yet to receive a federal response. For example, Recommendation 7.5 from the 2020 Report to Congress asked for the protection of consumers with Alpha-gal Syndrome, a life-threatening allergy to food, medications, and other products containing ingredients derived from mammals, by labeling these products clearly (Tick-Borne Disease Working Group, 2020). This third Report to Congress highlights issues that still require attention and identifies new areas in need of federal funding and resources.

New Challenges and Opportunities

In addition to the issues identified in the 2018 and 2022 Reports to Congress, the past several years have brought to the fore new areas for consideration, including health equity and the similarities between symptoms due to long COVID and those due to Lyme disease–associated chronic illness.

Health Equity

Health equity is a complex term, and although many definitions exist, the Robert Wood Johnson Foundation definition is both comprehensive and clear:

> "Health equity means that everyone has a fair and just opportunity to be as healthy as possible. This requires removing obstacles to health such as poverty, discrimination, and their consequences, including powerlessness and lack of access to good jobs with fair pay, quality education and housing, safe environments, and health care." (Braveman et al., 2017)

Health disparities—that is, differences in access to care, longevity, rates of disease, disease severity, disability, quality of life, and death (CDC, 2020a)—are the result of structural and societal determinants of health inequity (Solar & Irwin, 2010). Although health inequities are often associated with race, ethnicity, or sexual orientation, they also arise in the context of specific marginalized or stigmatized medical conditions such as mental health conditions, HIV/AIDS, substance use disorders, sexually transmitted infections, and tick-borne diseases and associated illnesses.

Issues of health equity and disparity are underscored throughout this report. However, simply identifying the inequities encountered by a group is not sufficient; efforts to eliminate these inequities should be concerted and sustained, and progress should be measured through the metric of health disparities (Braveman, 2014). The Working Group employed an intentional approach to ensure that the recommendations in this report address these issues in meaningful ways.

COVID-19

Many patients who have experienced a SARS CoV-2 infection report persistent symptoms that are highly debilitating and of unclear etiopathogenesis, a condition referred to as long COVID. These symptoms include fatigue, post-exertional malaise, and cognitive impairment. Long COVID is generally believed to be caused by either long-term damage to tissues (e.g., lung, brain, and heart) or pathological inflammation from viral persistence, immune dysregulation, or autoimmunity (Yong, 2021). The most common persisting symptoms in long COVID are also frequently reported in patients diagnosed with Lyme disease and other tick-borne illnesses. Given this array of overlapping symptoms, studies that examine the clinical similarities and etiopathogeneses for long COVID and other infection-associated chronic illness may provide insights into improved clinical management of patients experiencing tick bite–associated chronic illness. Current interest in long COVID provides a unique opportunity to leverage both new knowledge and research opportunities to advance understanding of tick bite–associated chronic illness.

Conclusion

The eventual control of tick-borne diseases and associated illnesses and improvements in care will require a sustained effort from multiple stakeholders including governmental agencies, researchers in

academia, industry and the community, health care workers, educators, and patients, including those from at-risk populations. In this report, the Tick-Borne Disease Working Group presents what it considers to be the key priorities for controlling tick-borne diseases and associated illnesses and improving the care and quality of life for affected individuals.

Chapter 2
Public Comments

A critical element of Report to Congress development was the incorporation of public commentary into the recommendations and subcommittee reports of the Tick-Borne Disease Working Group. Public commentary was received through emails delivered to tickbornedisease@hhs.gov, written comments submitted for each public meeting and published on the Working Group webpage, and verbal comments delivered at such meetings. Public commenters raised a multitude of issues and included patients, family members, and caregivers; advocacy groups; clinicians; researchers; health officials; and representatives of professional organizations. The Office of Infectious Disease and HIV/AIDS Policy, with the direction and input from members of the Working Group's Public Comments Subcommittee, conducted a brief analysis of the emails received since the inception of the federal advisory committee (FAC) (i.e., the Working Group).

Methods

Public comments were routinely distributed to Working Group members throughout the drafting of their subcommittee reports and the Report to Congress. The emails and comments were collated and counted with duplicates removed. The files were uploaded to a qualitative analysis software application, NVivo 12.0 Plus (QSR International), for coding and analysis (Wong, 2008). A pre-determined set of thematic and case codes were applied by one coder. The codebook was updated throughout the analysis process as themes and cases emerged in the content. Microsoft Excel Version 2018 was used to augment the reports created by NVivo.

Demographics

The analysis spanned a total of 2,082 written comments received during the Working Group's six-year tenure. Of those, 1,535 were classified as email and 547 were written comments submitted for public meetings. Of the 1,535 emails, 734 (48%) were submitted during the first cycle, from 2017 to 2018; 501 (33%) during the second cycle, from 2019 to 2020; and 300 (20%) during the third and final cycle, from 2021 to 2022. Of the 547 written comments, 194 (35%) were submitted during the first cycle, 247 (45%) during the second cycle, and 106 (19%) during the third cycle.[1]

A significant portion of the emails (greater than 98 percent) were uniquely written messages to the Working Group describing a personal story or the impact of tick-borne disease, requesting

---

resources, or commenting on the function of the Working Group.

A limited number of commenters were granted three minutes to speak at each of the Working Group's public meetings. Approximately 230 verbal comments were received by this means (Figure 3). Verbal commentary was excluded from this analysis.

Commenter Content by Illness

A significant portion of comments addressed Lyme disease (borreliosis), followed by tick-borne disease generally and Alpha-gal Syndrome (AGS) (Figure 4). Many, if not most comments, addressed more than one condition and the compounding impact of co-infections.
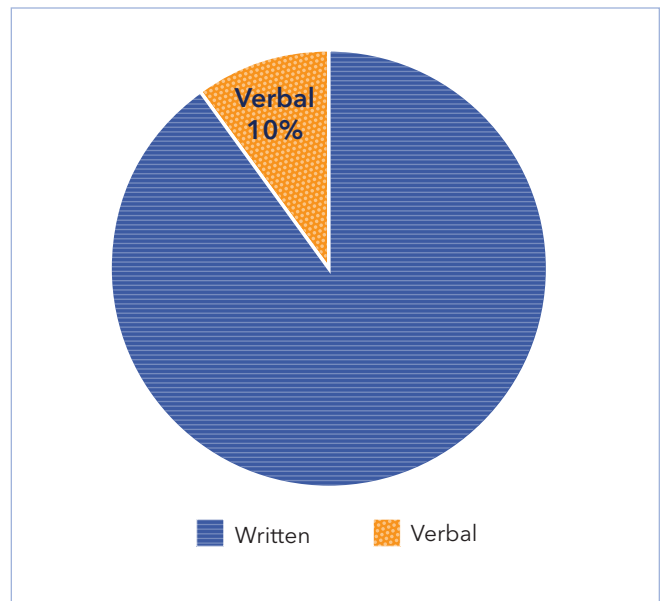
Figure 3. Type of commentary directed to the Tick-Borne Disease Working Group.
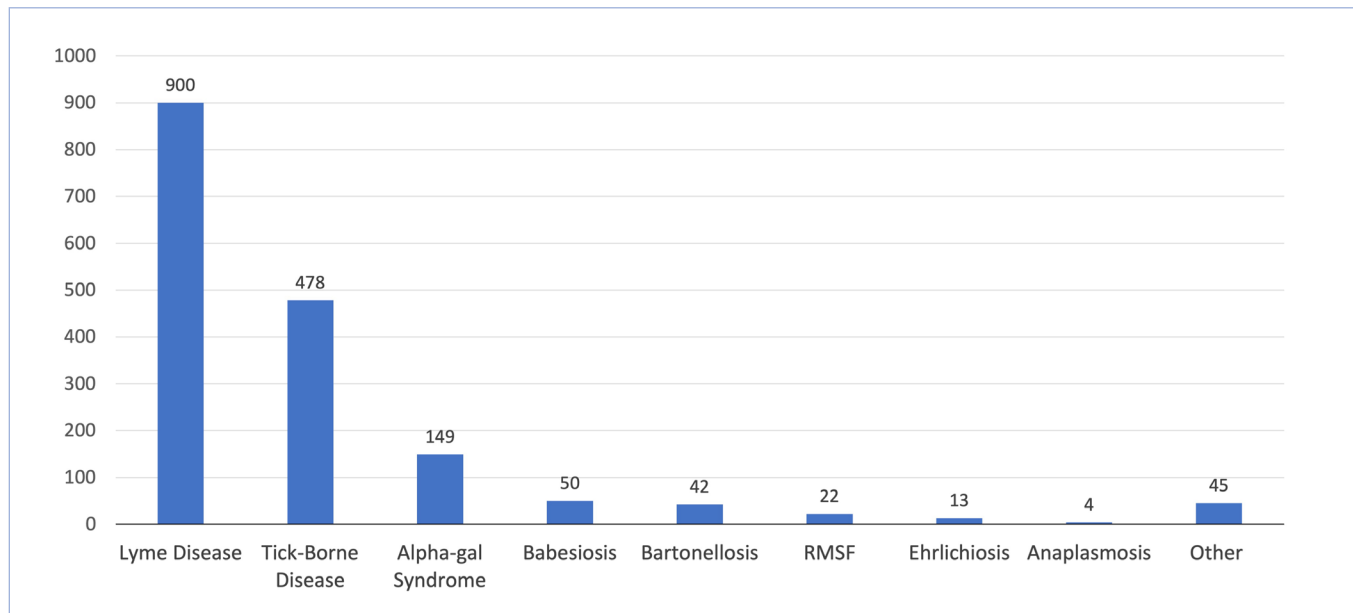
Figure 4. Commenter content by illness.

Note: Other includes Heartland, Bourbon, and Powassan viruses, STARI, and tularemia.

Dominant Themes

Themes (or topics) are concerns and sentiments that were repeatedly raised by the commenters. A codebook was populated with known themes from the current and previous Working Groups' papers, meetings, and discussions and then supplemented as new themes emerged during this public comment analysis process. The public comments were iteratively analyzed to ensure universal application of the final codebook. Figure 5 depicts the themes (topics) that were identified during this exercise, grouped into seven major categories: Challenges, Epidemiology, Ethics, FAC Business, Morbidities, Patient Experience, and Resources.
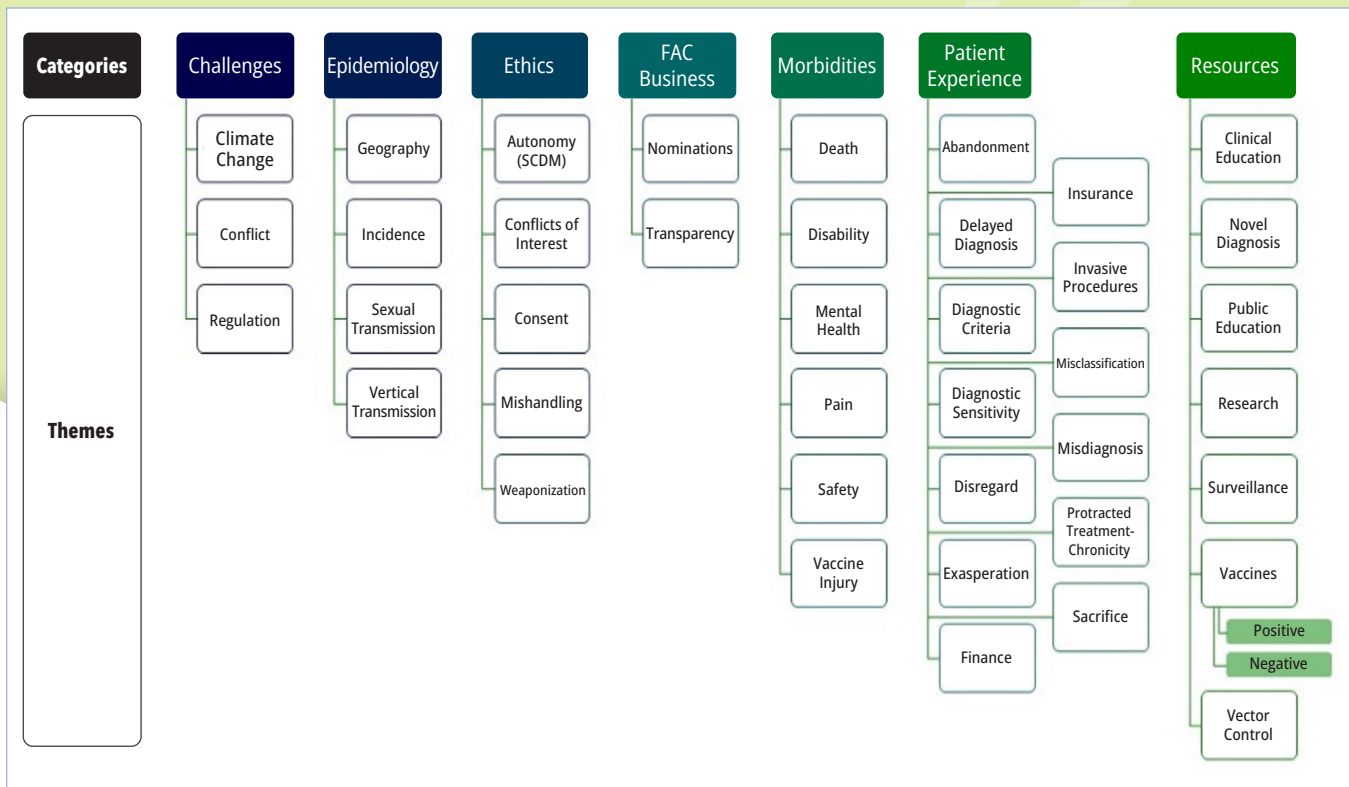
Figure 5. Coding themes/topics used to organize themes.

The following themes were expressed most frequently and by a wide variety of commenters: Need for Clinical Education, Feeling of Being Disregarded, Frustration with the Use and Application of Diagnostic Criteria, Clinical Reliance Upon Geographic Endemicity, Personal Sacrifice and Loss, Mental Health, Ethical Lapses or Mishandling by Governmental Entities, and Vaccines. These dominant themes are explored further in the following sections.

Need for Clinical Education

The need for more clinical education on tick-borne diseases and associated illnesses was consistently raised in public commentary. One commenter, Kristi Honaker, described her experience with AGS:

> My doctors don't know what medicines are safe, nor do they really care. They have never heard of my allergy so they think I am exaggerating. Pharmacists can't check to see if my allergens are in the medicines that I am prescribed. Dentists don't know how to treat someone with my allergy. Many medical professionals cannot be bothered to learn from their patient, whether or not that

patient has extensive knowledge on the subject. The list goes on forever. The medical community needs to be educated on how to deal with this allergy, especially since it is spreading so rapidly.

Other commenters reported similar experiences. They emphasized the lack of knowledge among providers, the frustration of having to explain their illness many times during a single medical visit, the confusion over diagnostic criteria, and the improper use of criteria for certain tests for tick-borne disease, among others. In general, commenters noted that clinicians often

- think of tick-borne diseases or illnesses as rare;
- believe it is impossible to become infected in areas considered to be low incidence;
- express skepticism when patients suspect tick-borne diseases or ask to be tested for them;
- are unaware of the existence of certain tick-borne illnesses (particularly AGS); and
- lack current knowledge of diagnosis or management of tick-borne diseases and associated illnesses.

The themes of misdiagnosis and delayed diagnosis also arose frequently in public comments, which further underscores the need for more clinical education.

Feeling of Being Disregarded

Another consistent and dominant theme is the feeling of being disregarded by clinicians and others involved in patient care. Commenters described being dismissed by providers, being accused of lying, or being told that their signs or symptoms were imagined or unrelated to a tick-borne illness. This disregard often led to delays in diagnosis or treatment and in some cases caused anxiety, frustration, or distress. These dismissive attitudes prevented some patients from seeking additional care for fear of further dismissal.

Commenters noted that they also experienced feelings of disregard when explaining their illness to friends, family, and employers. In one example, Anonymous states, "I have had Alpha-gal and Lyme disease for 7 years now. I suppose I will live the rest of my life being sick and receiving inadequate care, mainly because the doctors say that Alpha-gal is so rare, they have never seen a case and because no doctor takes Lyme seriously. They just don't believe me, either about AG or Lyme. They say it is not possible." Some commenters described being told that "There is no such thing" or "You're wrong," and others reported being referred to mental health care providers.

Frustration with the Use and Application of Diagnostic Criteria

Commenters expressed consternation and frustration about the seemingly arbitrary application of tick-borne disease diagnostic criteria. Specifically, they described situations in which clinicians had disregarded known signs and symptoms of tick-borne diseases. Jennifer Burton noted: "Most of us who have been bitten by any tick and end up with a large welt, rashes, fevers, fatigue, flu-like symptoms or even the classic 'bullseye rash' and seek medical attention are either discounted completely, told tick diseases

are rare or are not given the proper dosage of the recommended protocol for a long enough period of time to stop further illness."

Other commenters mentioned that clinicians did not adequately explain the criteria they used to arrive at their conclusions, or that different interpretations of diagnostic tests exist. Some noted that this issue was akin to lack of informed consent and that clinicians should explain their approach to diagnosis and the evidence used to decide on a patient's care plan.

Some commenters highlighted that clinicians often consider the erythema migrans (EM) rash, or "bull's-eye," as a requisite for the diagnosis of Lyme disease. One commenter stated: "The clinical diagnostic criteria for Lyme disease are too stringent, with only objective signs of the disease, such as an erythema migrans rash, arthritis, meningitis, or carditis, considered relevant." The reliance on the EM rash for the diagnosis of Lyme disease can lead some clinicians to dismiss other non-EM rashes. One commenter wrote: "I was bit by a deer tick in 2006. I recall removing it and recognized it to be a deer tick versus the dozens of wood ticks I'd pulled out of me growing up in the woods of northwest Wisconsin. I don't remember getting a classic bull's-eye rash, although the bite was behind by left knee so I could have missed it. It wasn't tested, and although I mentioned it to my doctor, no testing or follow up was done." Many other commenters described their clinicians' refusal to investigate potential tick-borne infections or diseases because of the absence of an EM rash.

Lastly, commenters noted the inappropriate use of the surveillance case definition in a clinical setting. Jill Auerbach summarized this sentiment: "The surveillance case definition is used like the Bible by healthcare workers causing so many unnecessary horrid results."
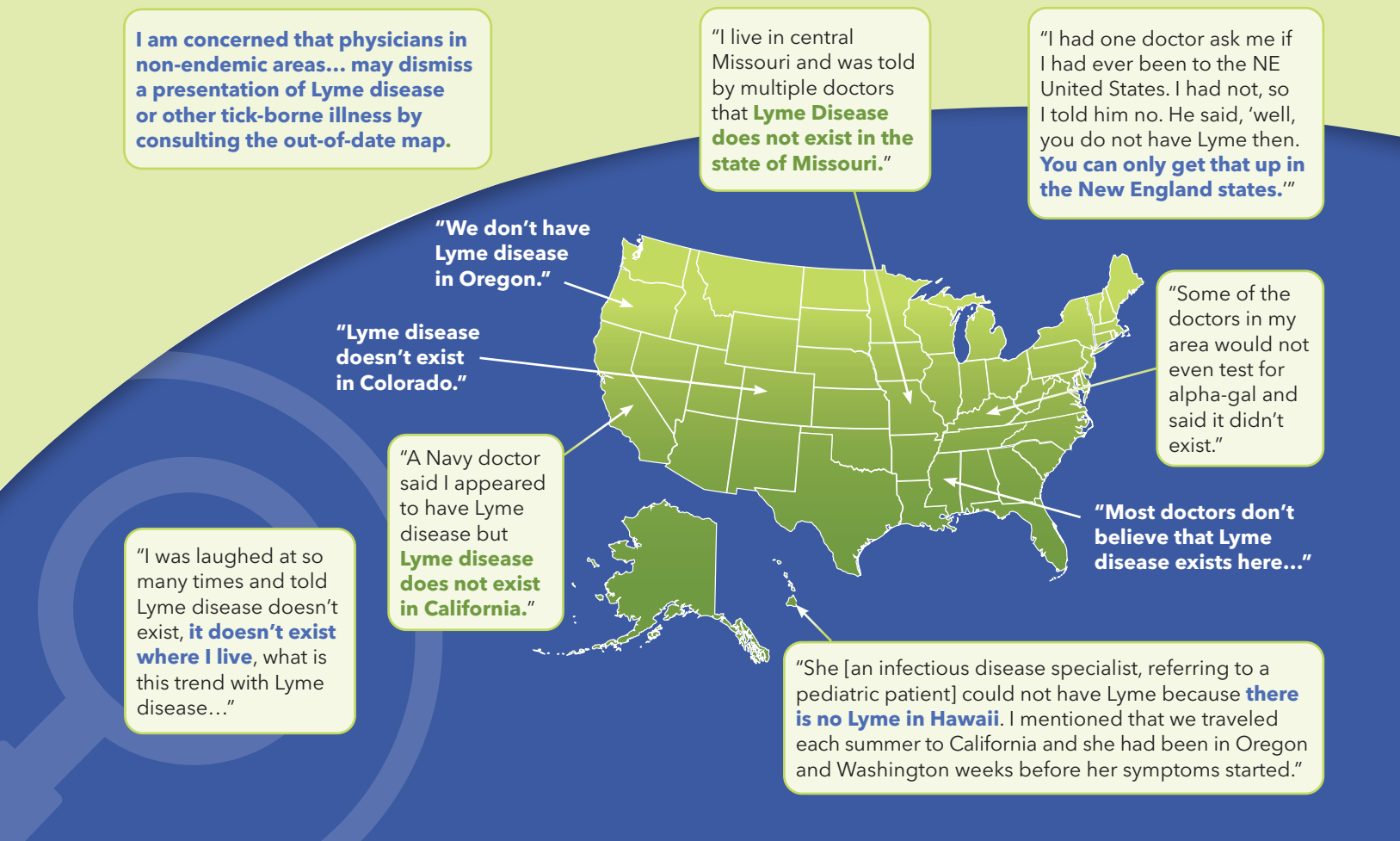
Figure 6. Selected commentary related to the geographic spread of tick-borne diseases and associated illnesses.

Note: In some cases, commentors who had indicated they had been diagnosed with multiple tick-borne infections referred subsequently to their infections as "Lyme." Please note that this term could encompass multiple infections.

Clinical Reliance Upon Geographic Endemicity

Many commenters raised the issue of the geographic spread of tick-borne diseases and associated illnesses. Some expressed fear about the incidence of tick-borne disease in their region or worry that further geographic spread may put more people at risk of contracting a tick-borne disease.

In general, commenters expressed frustration about clinicians' reliance on geographic endemicity in the diagnosis of tick-borne diseases and associated illnesses (Figure 6). Some commenters noted that they were exposed to ticks in other regions of the country or traveled or moved since initial exposure. These comments further underscore the need for enhanced clinician education.

Separately, commenters expressed frustration with currently available surveillance data and how they are presented. Many stated that the surveillance maps presented by the federal government create the false impression that ticks carrying human disease do not exist in areas of low incidence. Others claim that the current surveillance data are out of date and inconsistent with scientific literature.

Finally, commenters noted that although the spread of Lyme disease is receiving more attention and resources, other tick-borne diseases and associated illnesses, such as AGS, remain poorly understood. Some commenters requested the investment of additional resources in the surveillance of low-incidence tick-borne diseases and illnesses to better characterize their geographic spread.

Rhisa Parera

I saw dozens of doctors who treated me for depression before I went to a doctor who told me she thought I may have Lyme disease. … It's already tough getting clear answers within Western Medicine, but add being a woman—a black woman—a black Latina and it seems like there is no help in sight. I'm hoping my story can change that.

For years I struggled with my health, alone. Getting a Lyme diagnosis is hard. I had seen dozens of doctors, specialists, with no answers, FOR DECADES. **It was such a confusing situation because how do you explain to someone who doesn't get it that you are sick but all these doctors are saying you're fine?** You start to think you're insane and that other people will think the same so you isolate and start to pull away from people.

Personal Sacrifice and Loss

Tick-borne diseases and associated illnesses impact people in numerous and consequential ways. Individuals wrote about the detrimental effect on their marriages and personal relationships and on their ability to start new relationships after diagnosis. Some described difficulty maintaining employment and steady income, despite the heightened need for health insurance or other benefits. Many individuals have experienced difficulty in obtaining new positions or seeking promotions because of the time off needed for medical appointments and illness. Young commenters and their parents described the impact of their condition on school and educational opportunities. Finally, commenters explained that the denial of insurance and disability claims leads to stress and anxiety.

A common result of these collective sacrifices is a sense of isolation. One anonymous commenter, suffering from AGS, noted: "My husband, and I have always loved being outdoors, working in the yard, traveling, camping, hiking, kayaking, fishing etc. Now, I cannot safely do any of those things for fear of another tick bite that could cause my reactions to escalate. I can also no longer enjoy BBQs with family and friends, eating out at restaurants due to the danger of cross contamination/fumes."

Other losses were described as catastrophic. Individuals wrote about the immense disruption that a patient with tick-borne disease can experience, from emergency and intensive medical care to accommodations related to personal and workplace needs. Several parents wrote to the Working Group to describe the loss of their children to tick-borne disease.

Impact on Mental Health

The collective impact of these sacrifices and loss highlight the critical need to acknowledge the mental health implications of tick-borne diseases and associated illnesses. Psychiatry specialist, Dr. Robert Bransfield noted, "The TBDWG has not yet addressed the chronic psychiatric consequences of Tick-Borne Diseases. In order for the TBDWG to fulfill their

responsibility to the public it is important to address the causal association between Lyme/Tick-Borne Diseases and psychiatric symptoms."

Commenters diagnosed with tick-borne diseases and associated illnesses reported experiencing anxiety, depression, and suicidal ideation or attempted suicide. Stephan and Mary Jane Heppe wrote to the Working Group about the death of their son:

> Our son, Vaughan Heppe, died last October as a result of Lyme-induced encephalopathy. … This disease and lack of access to care took everything away. Because of his brain inflammation, mental illness set in, and Vaughan lost hope. He committed suicide last October 2, 2017.

Other commenters noted that clinicians must better address both the physical and mental needs of those diagnosed with tick-borne disease.

Ethical Lapses or Mishandling by Governmental Entities

Pervasive skepticism and mistrust of the government were evident in many public comments. Individuals claimed that the federal government is not fulfilling its mission to protect the public from a known public health threat. They noted a lack of interest and investment in tick-borne diseases and associated illnesses, especially compared to Zika virus and COVID-19. Other commenters believe that the government is actively hiding truths about tick-borne diseases from the public. These comments often alleged scientific fraud and a coverup. Many comments called for a congressional investigation of the "mishandling of Lyme disease."

Issues with Vaccines

This skepticism manifested in distrust of the regulation of tick-borne disease vaccines, and the LYMERix vaccine in particular. Some commenters claimed that vaccines were created solely for profit and that the government approved LYMERix for inappropriate reasons. Others expressed that adverse events and potential complications possibly resulting from vaccination have not been thoroughly investigated. Many commenters worry that the vaccine mechanism, which may be used in future vaccines, is problematic.

Other commenters took a different approach and strongly recommended the need for vaccines to prevent tick-borne disease. Some believe that a vaccine is an important public health tool that is cost-effective and not reliant upon individual behavior. Some complained that the federal government has not invested sufficiently in vaccine candidates and vaccine research.
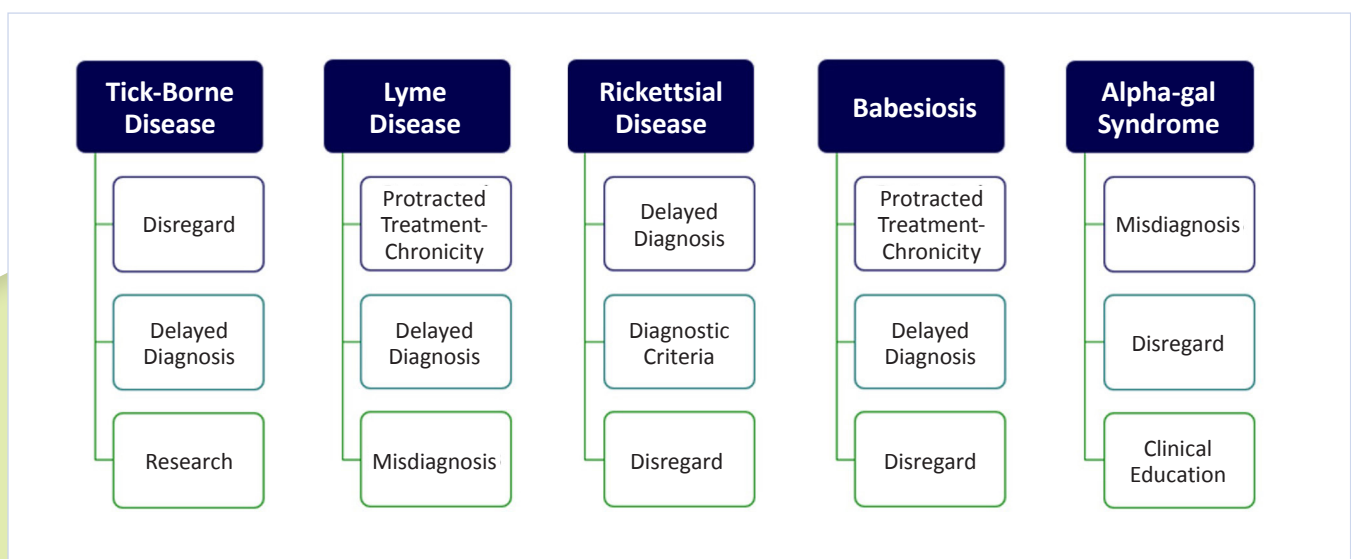
Figure 7. Common themes by illness.

Themes by Illness

Certain themes emerging from the analysis were specific to individual illnesses. For commenters that primarily addressed borreliosis, including Lyme disease and tick-borne relapsing fever, the themes of Protracted Treatment, Delayed Diagnosis, and Misdiagnosis dominated. Some themes specific to an illness overlapped with those described previously (i.e., Feeling of Being Disregarded, Need for Clinical Education, and Need for Research). Figure 7 captures the themes that were directly attributed to a specific illness or to tick-borne diseases in general.

Limitations

The primary limitation of this analysis is that the content was coded and analyzed by a single person. Opportunities to compare and delineate themes, eliminate potential researcher bias, and offer multiple perspectives or interpretations is therefore also limited.

Another significant limitation is the selection bias of those who elected to provide comment to the Working Group. These individuals may not fully represent the body of all individuals affected by or diagnosed with tick-borne diseases and associated illnesses.

Some of the material, by request of the commenter, or by guidelines provided by the Office of General Counsel, was redacted. Some of the redactions made it difficult to determine unique emails, determine locations referenced in the text, and interpret some of the themes described in comments.

Due to delays in setting up the first cycle of the Working Group, commentary from that period is limited. Further, public comments from the third cycle are limited to those received through October 11, 2022, because of the need to finalize language for publication in the third Report to Congress.

Chapter 3
Access to Care and Education

Patients with tick-borne diseases and associated illnesses experience multiple inequities in health care access, chief among these is limited access to knowledgeable clinicians. Structural and societal determinants of health interact to produce three interwoven types of barriers: patient-encountered, clinician-encountered, and medical educational. The limited availability of high-quality educational opportunities reduces the number of clinicians who understand the nuances of tick-borne diseases and increases the professional scrutiny that they face. The professional risks and demanding duties of caring for patients with complex tick-borne illness further restricts the ranks of clinicians who are willing to assist these patients, giving rise to disparities in access to care. This chapter describes the major challenges with each barrier in order to demonstrate a common root cause as well as several shared solutions.

Recommendations

Recommendation 3.1: Provide funding for the U.S. Department of Health and Human Services to sponsor the National Academy of Medicine (NAM) within the National Academies of Sciences, Engineering, and Medicine to conduct an objective, comprehensive review of the basic science and clinical evidence for diagnosis and treatment of Lyme disease, with emphasis on acute and Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD). The purpose for conducting an objective review would be to establish what is definitely known, what is partially understood, and what remains unknown about Lyme disease. The review mechanism shall be transparent and include public stakeholders and patient representatives, experts in trial design and execution, as well as a diversity of experts who represent the full spectrum of scientific perspectives on Lyme disease. The expert panel will produce a comprehensive public report, which will be used to inform federal and state initiatives.

Rationale

Lyme disease accounts for the vast majority of tick-borne disease cases and tick-borne disease-related controversies. Many aspects of disease pathogenesis and facts regarding the effectiveness of treatment at various time points in the infection are unclear, unrecognized, or disputed. The purpose for conducting an objective evidence review, using subject matter experts on Lyme disease and experts on trial design and execution, would be to establish what is definitely known, what is partially understood, and what remains unknown about Lyme disease. Thus, the NAM report would be used to inform government policies, research grant processes, and educational outreach to clinicians and the public.

Within the Lyme community, there is significant distrust regarding how the science has been evaluated in the past and conveyed to clinicians. The transparent nature of the proposed review should engender trust in its findings. The key element for success will be to select NAM reviewers who can focus solely on evaluating all of the pertinent scientific findings.

Although many Lyme disease–related topics would benefit from such a review, a reasonable starting point would be to review the evidence regarding U.S.

patients with erythema migrans, the largest group of all reported cases, and PLD/CLD, the topic that generates the most controversy. Information gained in the review of variations in clinical presentation may prove useful for reducing the risk of patients developing PLD/CLD.

Meaningful stakeholder engagement in the evidence review is also crucial to the findings being accepted by clinicians and the public. For example, in the case of PLD/CLD, stakeholders should include (a) patients, caregivers, or patient advocates who can meaningfully represent the acute and PLD/CLD perspectives; (b) clinicians (including clinicians who treat patients with acute and PLD/CLD as well as those who are subject matter experts in acute and PLD/CLD education); and (c) research scientists with expertise and experience that represent diverse scientific perspectives on the full spectrum of Lyme disease. Similar stakeholder groups would be necessary for content related to other aspects of Lyme disease.

Recommendation 3.2: **Upon activation of Recommendation 8.1 of the Tick-Borne Disease Working Group 2022 Report to Congress outlining implementation of Working Group priorities[2], the first recommendations to be discussed for updates and public input are Recommendations 7.1 and 7.2 from the Tick-Borne Disease Working Group 2020 Report to Congress that address educational materials and web content. Emphasis should be placed on receiving input via meaningful engagement with stakeholders on how these recommendations have been implemented to date across HHS operating divisions and how well they reflect the current state of the science.**

Rationale

Several Department of Health and Human Services (HHS) agency websites include content related to tick-borne diseases and Alpha-gal Syndrome

(AGS). However, the content does not represent the current state of the science. The existence of significant scientific uncertainty and the lack of acknowledgement thereof on federal websites and training programs contribute substantially to the professional barriers with which clinicians must contend. The content of the federal websites and training pertaining to Lyme disease and other tick-associated illnesses should represent the primary literature as it is—both strengths and weaknesses—and identify scientific gaps. For PLD/CLD, it should also inform clinicians of the divergent scientific perspectives, thereby opening the door to the use of clinical judgment and shared decision-making. Adopting these changes would reduce the pressure on clinicians who currently treat PLD/CLD, increase the knowledge base of front-line clinicians seeking guidance to inform their practice, and provide a more hospitable environment to attract new clinicians to care for this growing patient population.

For all websites with tick-borne disease content, thorough reviews conducted with meaningful stakeholder engagement in the development or revision of the content are needed. For example, in the case of acute and PLD/CLD, stakeholders should include (a) patients, caregivers, or patient advocates who can meaningfully represent the acute and PLD/CLD perspectives; (b) clinicians (including clinicians who treat patients with acute and PLD/CLD as well as those who are subject matter experts in acute and PLD/CLD education); and (c) research scientists with expertise and experience that represent diverse scientific perspectives on the full spectrum of Lyme disease. Similar stakeholder groups would be necessary for content related to other tick-borne diseases and AGS.

Recommendation 3.3: **Fund and support continued and ongoing modification of the federal government websites, starting with the CDC and NIH websites, as well as educational materials and**

---

[2]Recommendation 8.1 (p. 75) requests that HHS's Office of the Assistant Secretary of Health (OASH) convene regular virtual public co-creation or collaboration workshops and technical consultations, in concert with relevant HHS operating divisions (CDC, FDA, NIH, and CMS) and with other relevant federal departments to share updates and receive input on progress made toward implementing FAC recommendations from the three reports to Congress.

seminars for clinicians, the public, and public health departments to reflect the current state of the science related to Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD), which is limited, emerging, and unsettled, and to acknowledge that there are divergent views on diagnosis and treatment of patients with PLD/CLD.

Rationale

Modifications to government websites and educational materials that acknowledge the scientific uncertainty regarding PLD/CLD will promote health equity by reducing the professional barriers experienced by clinicians and allowing clinicians and patients to engage in shared decision-making with the goal of individualizing care and optimizing outcomes. When this report was written, the following language—which serves as a good example of what needs to be incorporated on all federal websites and educational materials—had been recently added to a Centers for Disease Control and Prevention (CDC) webpage:

> Some patients report persistent symptoms of pain, fatigue, or difficulty thinking even after treatment for Lyme disease. The state of the science relating to persistent symptoms associated with Lyme disease is limited, emerging, and unsettled. Additional research is needed to better understand how to treat, manage, and support people with persistent symptoms associated with Lyme disease. In light of these research gaps, recommendations for treatment of persistent symptoms in people previously treated for Lyme disease are not provided here. (CDC, 2022e)

Recommendation 3.4: **Provide the HHS Secretary with discretionary authority to maintain telehealth flexibilities independent of Public Health Emergency declaration for patients with tick-associated illnesses in order to ensure access, parity, and equity for those receiving in-person and telehealth services.**

Rationale

Access to care issues are not unique to tick-borne disease patients and have been addressed successfully in other communities using telehealth. For example, telehealth has helped rural communities address workforce shortages and reduce the burden on patients who might otherwise have to travel long distances for specialty care. Because of the COVID-19 pandemic, telehealth is now widely accepted by patients and providers. Telehealth flexibilities will ensure that individuals with tick-borne disease illness have access to appropriately trained clinicians by bridging gaps in the current PLD/CLD clinician workforce. Patients in the Lyme disease community have come to rely on telehealth to increase their access to care and would be detrimentally impacted if it were no longer available.

Recommendation 3.5: **Fund, support, and encourage community-based participatory research programs for persistent Lyme disease/chronic Lyme disease (PLD/CLD) and complex presentations of late Lyme disease and other tick bite–associated illnesses. This includes the development and growth of community research capacity to accelerate the fundamental knowledge base using "big data" registries, data-sharing platforms, specimen and tissue sample repositories, and genomic and precision medicine approaches that reflect the underlying heterogeneous nature of tick-borne diseases and associated illnesses.**

Rationale

Tick-borne diseases and associated illnesses are research-disadvantaged. Promoting innovative research methods aligns with the NIH Strategic Plan for Tickborne Disease Research and may maximize the impact of the available funding. Community-based participatory research (CBPR) approaches, such as those utilized by the National Institute on Minority Health and Health Disparities of the National Institutes of Health (NIH), successfully advance the knowledge base for research-disadvantaged diseases.

Health equity "is optimal health for all" (American Medical Association, 2018). According to CDC, health care equity is achieved only "when every person has the opportunity to attain his or her full health potential" and when no one is "disadvantaged from achieving this potential because of social position or other socially determined circumstances" (CDC, 2020a). Thus, health equity is a matter of fairness and moral justice; groups experiencing disparities are often marginalized or lack political, social, or economic power (American Medical Association, 2018; Liburd et al., 2020).

Health disparities—differences in access to care, longevity, rates of disease, disease severity, disability, quality of life, and death (CDC, 2020a)—are the result of structural and societal determinants of health inequity. **Structural and social determinants of health** act systematically through "long causal chains of mediating factors" (Solar & Irwin, 2010). Institutions, policies, and practices, including governmental policies and practices, that determine the distribution of power, funding, and the availability of services are structural determinants of health. Social determinants of health—economic stability, education access and quality, neighborhood and built environment, social and community context, and health care access and quality—result from structural determinants and act within the context in which people live their lives (Office of Disease Prevention and Health Promotion, n.d.).

Background

"The ultimate test of the quality of health care is whether it helps the people it intends to help" (IOM, 2001).

Health Equity Has Eluded Many Patients with Tick-Borne Diseases and Associated Illnesses

Many patients with one or more tick-borne illnesses face daunting health disparities including decreased quality of life (Johnson et al., 2014; Rebman et al., 2017), increased rates of disease (Fallon et al., 2021), increased disease severity (Dennison et al., 2019), preventable death (CDMRP, 2022; Dahlgren et al., 2012; Marx et al., 2020), and limited access to care (Johnson et al., 2011). Resolving limitations to accessing quality care could substantially reduce the other health disparities.

Health disparities related to tick-borne illnesses exist along racial, ethnic, and socioeconomic lines. One frequently cited study found that in a high-incidence area for Lyme disease, the incidence of Lyme arthritis, a late manifestation, was higher in Black people than White people, while White people had higher rates of reported erythema migrans (EM) rash, an early manifestation (Fix et al., 2000). It has been hypothesized that under-recognition of EM in people of color and implicit bias toward Black people may contribute to the diagnostic delays in this population (Dennison et al., 2019; Fix et al., 2000; Hall et al., 2015). Like Black people, Hispanic people are more likely than non-Hispanic people to present with manifestations of disseminated disease and less likely to have a reported EM (Nelson et al., 2016). Treatment failure rates are generally higher for patients presenting with delayed diagnosis and late manifestations than for

patients with EM rashes (Hirsch et al., 2020; Logigian et al., 1999; Steere & Angelis, 2006; Steere et al., 1994). These inequities may be a function of differences in Lyme disease awareness, language barriers, and limited access to health care (Nelson et al., 2016). Given that roughly 40% of employees in high-risk occupations such as landscaping-related services and farming are of Hispanic ethnicity, this finding has important implications (Nelson et al., 2016). The effect of socioeconomic status varies by tick-borne disease. One study found that counties with lower poverty and crime rates and higher levels of education had a higher incidence of Lyme disease, while counties with higher unemployment, less educated populations, and lower crime rates were associated with a higher incidence of human monocytic ehrlichiosis (Springer & Johnson, 2018).

Potential for Sex-Based Health Disparities

Various aspects of Lyme disease appear to affect males and females unequally. A prospective study of adult patients with EM lesions measuring 5 cm or more found that the average EM size was 2.18 cm larger in males than in females (Rebman et al., 2021). Because the CDC surveillance case definition for Lyme disease requires that an EM measure 5 cm or more to be a reportable case, it is unclear whether sex-related differences in EM size prevent women from meeting that criterion and delay or preclude the diagnosis by clinicians who apply the EM size criterion in their clinical practice. Although EM rates are similar for both genders, males are more likely than females to be diagnosed with Lyme arthritis, neuroborreliosis, and carditis (Rebman et al., 2015; Steere & Angelis, 2006; Strle et al., 2013), while females are more likely to develop and be diagnosed with persistent symptoms of Lyme disease (Aucott et al., 2022). The pathophysiology of Lyme arthritis, neuroborreliosis, and carditis is fairly well understood, and generally accepted treatment protocols exist for these presentations. However, that is not the case for persistent symptoms of Lyme disease, placing females at risk for decreased access to effective care and decreased quality of life. A study of Lyme disease in pregnant and non-pregnant women found that pregnant women were less likely than nonpregnant women to have a classic "bull's-eye" rash or present with constitutional symptoms such as fatigue, headache, myalgia, arthralgia, dizziness, nausea, and fever (Maraspin et al., 2020). These diminished symptoms/findings could place pregnant women at a disadvantage for being diagnosed early in their infections, when treatment is most likely to be successful, thereby increasing their risk of increased disease severity and poorer quality of life.

Major Challenges and Issues

Patient-Encountered Barriers to Obtaining Care

Patients with tick-borne diseases and associated illnesses encounter numerous barriers to accessing care, including structural barriers created by insurers and medical boards (Figure 8). These barriers to care were discussed extensively in the Tick-Borne Disease Working Group 2020 Report to Congress and are briefly summarized here:

- Many patients report that their care is not covered by insurance (Johnson, 2019a, 2019b; Johnson et al., 2011, 2014, 2020). For example, 18% of the participants in the MyLymeData patient registry report that they do not use antibiotics because their insurance will not cover them, and 50% of registry participants report that their clinicians do not accept insurance coverage (Johnson, 2019a). The registry consists of self-reported data for 3,903 U.S. patients diagnosed by a health care provider with Lyme disease obtained from November 2015 to November 2016.

- Many patients with a tick-borne illness cannot find local clinicians to treat them and travel great distances to obtain care from knowledgeable clinicians. In a survey of more than 2,400 Lyme disease patients, 60% of respondents reported traveling more than 50 miles for Lyme disease treatment, with 9% traveling more than 500 miles; 82% of PLD/CLD patients who sought care at their local hospital had difficulty obtaining treatment, and 51% saw seven or more clinicians before
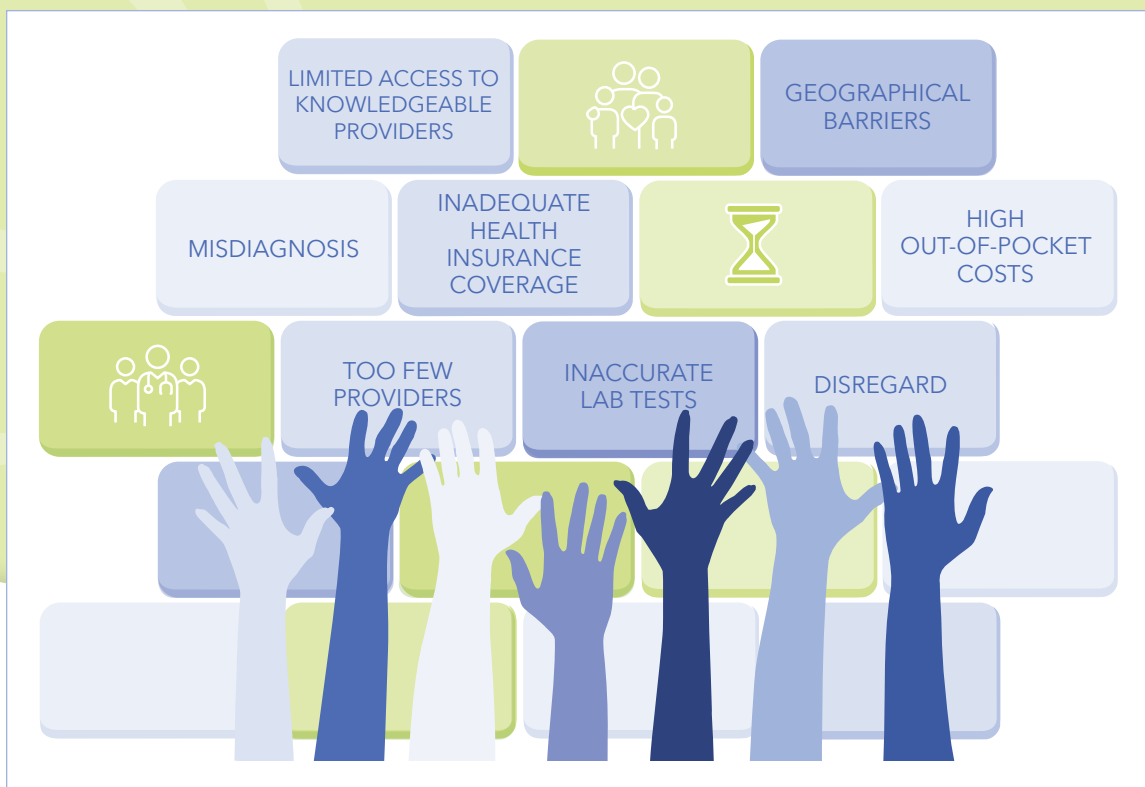
Figure 8. Patient barriers to care.

obtaining accurate PLD/CLD diagnoses (Johnson et al., 2011). In another survey with more than 3,000 respondents, 78% of patients with PLD/CLD experienced a diagnostic delay of six months or more (Johnson et al., 2014).

- Many AGS patients experience significant diagnostic delays. Semi-structured interviews of 28 AGS patients found that 80% experienced an average delay of 7.1 years, and less than 10% of more than 100 medical visits resulted in the correct diagnosis or appropriate referral (Flaherty et al., 2017).

Structural barriers also include policies and processes that exclude patients from meaningful participation in decisions that ultimately affect their ability to access quality care. Processes that determine funding for scientific research and the development of clinician educational content often exclude patients and their advocates from participating. In the case of research funding, grant review committees that lack meaningful patient engagement are less robust and may not recognize the importance of research avenues that directly address the lived experiences and priorities

of patients (Bendiscioli, 2019). In addition, the processes that funding organizations follow may divert funding away from novel and/or innovative approaches and topics that patients value (Bendiscioli, 2019). Scoring systems that award points based on researcher reputation and track record are "researcher-centric"; those that award points to research identified by patients as important to improving the quality of their lives are "patient-centric." Because patients are the ultimate end user of health care research findings and hence the most important stakeholder, their engagement is critical to achieving the primary goal of health care research—namely "to [improve] health by providing beneficial care to patients" (IOM, 2009). Meaningful patient engagement requires not only selecting patients or patient advocates qualified to represent the community, but also engaging them early enough in the process to make a difference in the process outcome or ultimate product (Johnson & Smalley, 2019).

The choice to include or exclude patients and patient advocates from funding decisions varies across

government entities. The Department of Defense's Tick-Borne Disease Research Program includes tick-borne disease advocates in its funding review process, while NIH does not (Davey, 2021; Purdue, 2021). The availability of clinicians knowledgeable about tick-borne diseases and associated illnesses directly impacts outcomes for tick-borne disease patients, yet patients and patient advocates have been excluded from meaningfully participating in the development of clinician undergraduate training or continuing medical education curricula. According to NAM, "the key goals of medical education include helping learners at all levels develop the ability to think critically and appraise the evidence for clinical decision making" (IOM, 2009). In pursuing these goals, outcomes that patients deem important are foundational (Johnson & Smalley, 2019).

Clinician-Encountered Barriers to Providing Care

The clinician supply and demand imbalance for patients with late presentations and PLD/CLD has been evaluated from the perspective of the patient (Johnson et al., 2011) but not the clinician. Clinicians caring for patients with complex cases of Lyme disease and PLD/CLD often navigate a variety of obstacles (Figure 9) (Johnson & Maloney, 2022). The lack of knowledgeable treating clinicians willing to provide care for patients with tick-borne diseases and associated illnesses is directly related to the structural and societal barriers that complicate or preclude care for this marginalized patient group. A 2021 survey of U.S. clinicians who treat PLD/CLD patients ("2021 Clinician Survey") was conducted by LymeDisease.org between September 23 and December 1, 2021, with
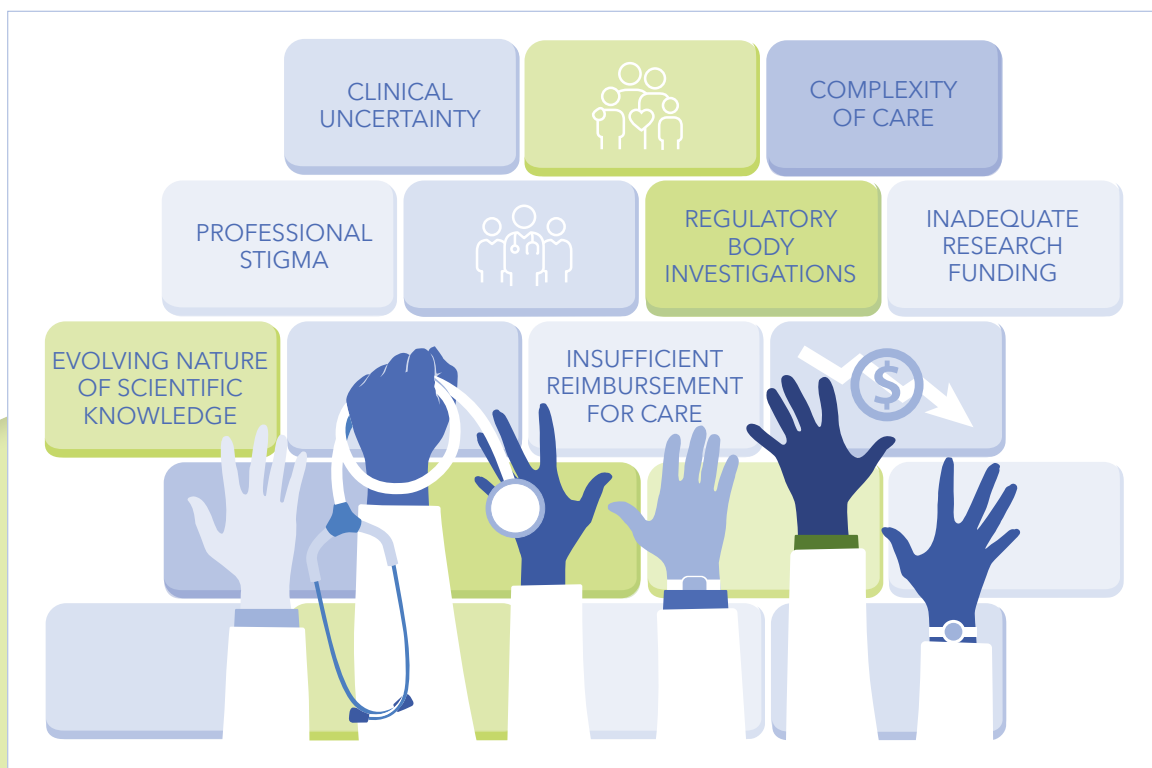

Figure 9. Clinician barriers to care.

the objective of characterizing the types of clinicians that provide care and the barriers they encounter (Johnson & Maloney, 2022). The organization distributed the survey through a variety of methods including its physician referral program and broader email outreach; 155 clinicians from 30 states responded. Clinicians responding to the survey identified the following challenges to providing care:

• Complexity of care (79%)

• Patients' inability to pay out-of-pocket costs (75%)

• Lack of professional support from colleagues (61%)

• Opposition to the treatment of PLD/CLD from some physician organizations (59%)

• Cognitive impairment of patients (57%)

• Frequent patient calls between scheduled appointments (49%)

• Reimbursement for care (34%)

• Length of visits (31%)

• Communication issues with patients (22%)

Scientific and Clinical Uncertainty

The gaps in scientific knowledge of tick-borne diseases and associated illnesses create uncertainty for clinicians who provide care for tick-borne disease patients, including PLD/CLD. In the 2021 Clinician Survey, 72% of respondents believed that diagnostic and therapeutic uncertainty are major challenges that prevent other clinicians from treating patients with PLD/CLD (Johnson & Maloney, 2022). Important scientific gaps include (a) disease pathogenesis of individual infections, concurrent tick-borne illnesses, and conditions such as AGS; (b) accurate diagnostic testing, especially for patients with PLD/CLD; and (c) optimal treatment approaches for patients with tick-borne diseases and associated illnesses.

As the scientific knowledge of tick-borne diseases continues to grow and evolve, many uncertainties remain. For example, the discovery of new pathogenic *Borrelia* species, especially *B. miyamotoi*, whose distributions and symptoms overlap with those of other tick-borne diseases, introduces diagnostic uncertainty (i.e., Does this patient have Lyme disease

or *B. miyamotoi* disease?). The expansion of tick ranges poses similar problems. The lone star tick (*Ambylomma americanum*), which is associated with southern tick-associated rash illness (STARI), is now widely distributed in the eastern United States (Kennedy & Marshall, 2021). Although the initial presentation of the illness is similar to acute Lyme disease, the pathogenic agent of STARI has yet to be identified, and no diagnostic tests for this infection exist. Thus, although the EM rash used to be considered pathognomonic for Lyme disease, when patients present with an EM rash in areas with established lone star tick populations, clinicians must also consider STARI as a potential diagnosis.

Diagnostic uncertainty has two main sources. Uncertainty related to clinical presentations is one. This includes the challenges posed by the overlapping clinical presentations of many tick-borne diseases and the highly variable presentations of disseminated Lyme disease and AGS. The limitations of diagnostic testing is the other. Point-of-care testing has limited availability, and many diagnoses are based on serologic tests, which can be inaccurate for many reasons (Bobe et al., 2021). It is important to recall that antibody responses in a given individual can fall outside established laboratory reference ranges for a population and yet the patient can still be infected (Aguero-Rosenfeld et al., 1996; Steere et al., 2008). With regard to PLD/CLD, no tests exist to demonstrate successful bacterial eradication or to confirm other potential etiologies for ongoing symptoms and signs (CDC, 2021b).

Therapeutic uncertainty remains a concern. For many tick-borne diseases, prevailing therapeutic regimens are based on clinical observations with little or no evidence from randomized controlled/comparative trials. Although the body of evidence for Lyme disease is greater than those for other tick-borne diseases, it is still quite limited, and the quality of that evidence is an important source of disagreement (Cadavid et al., 2016; Cameron et al., 2014; Hayes & Mead, 2004; Lantos et al., 2021; NIHCE, 2018). Indeed, the majority of GRADE (Grading of Recommendations, Assessment, Development, and Evaluations)-based evidence assessments regarding

treatment benefits determined that the evidence is generally of low quality (Cadavid et al., 2016; Cameron et al., 2014; Hayes & Mead, 2004; Lantos et al., 2021; NIHCE, 2018).

As other chapters in this report have described in detail, there is a critical need for increased research funding for basic science investigations and therapeutic trials to reduce the numerous gaps in the scientific evidence related to tick-borne diseases that result in clinical uncertainty. Patients, clinicians, and researchers would benefit from the discovery of accurate diagnostic biomarkers for all tick-borne diseases, including the potential etiologies of PLD/CLD, that are clinically valid across the entire spectrum of patients. This advance would reduce diagnostic uncertainty, thereby decreasing diagnostic delays, and make it easier to design and conduct clinical trials, which could lead to more successful therapeutic regimens. However, because most presentations are treated with generic antibiotics, the pharmaceutical industry, which typically funds therapeutic trials, has few incentives to conduct trials using generic drugs or to develop novel therapeutics. Thus, tick-borne diseases are research-disadvantaged diseases, similar to rare and orphan diseases. Despite this, NIH has historically allocated insufficient funds to investigate this group of diseases.

Professional Stigma and Risks Posed by Regulatory Bodies

Respondents to the 2021 Clinician Survey noted a lack of support from colleagues and professional stigma as important barriers to providing care; indeed, 75% reported having been stigmatized or treated disrespectfully by professional colleagues because they treat patients with Lyme disease (Johnson & Maloney, 2022). In addition, 85% stated that professional marginalization is preventing other clinicians from caring for patients with PLD/CLD. "Stigma is a powerful social process that is characterized by labeling, stereotyping, and separation, leading to status loss and discrimination, all occurring in the context of power" (Nyblade et al., 2019). Stigmatization and discrimination may be institutionalized in policies, procedures, or practices (such as guidelines). Clinician marginalization reduces opportunities for sharing on-call and hospital responsibilities and stifles information sharing. Exclusion from insurance networks, limited opportunities to share office space, and disparagement by colleagues are examples of stigmatization.

Clinicians reported that the potential for investigation by regulatory boards is wearing and that defending oneself requires valuable time, energy, and funds (even when sanctions are not imposed). Further, investigations are often protracted for years, and clinicians may suffer revenue losses when investigations intrude on clinic operations.

State medical boards, hospital credentialing committees, and insurer quality committees may be ill-equipped to judge care when a medical field is evolving and relevant trial evidence is scarce. Although many of these bodies rely on their own perception of the "standard of care" and prevailing clinical practice guidelines (CPGs), these metrics are of limited use in Lyme disease because the evidence base is weak and treatment approaches diverge (Johnson et al., 2018).

Some regulatory decisions to sanction clinicians who treat patients with tick-borne diseases may reflect regulators' misconceptions regarding the available evidence, misunderstandings regarding the principle and practice of evidence-based medicine, and misgivings or a lack of appreciation of shared decision-making. The Tick-Borne Disease Working Group 2018 and 2020 Reports to Congress identified several clinician knowledge gaps, including the following:

- Insufficient understanding of the spectrum of clinical presentations of tick-borne diseases and associated illnesses;
- Underestimation of their patients' risk of Lyme disease;
- Misconception that patients who do not meet CDC's surveillance case definition cannot have Lyme disease;

- Insufficient education regarding the limitations of diagnostic testing for tick-borne diseases, including the potential for false positives and false negatives; and

- Lack of understanding regarding treatment (Access to Care Services and Support to Patients Subcommittee, 2018; Training, Education, Access to Care, and Reimbursement Subcommittee, 2020).

When self-identified or designated experts are not fully aware of the pertinent research evidence and harbor some or all of the knowledge gaps described above, the likelihood that they will primarily support their opinions by relying on popular third-party sources such as CPG increases. The inherent problem with this approach is that CPG recommendations often provide a generalized, population-based approach to patient management that cannot account for the details of an individual patient's circumstances, treatment needs, or values and preferences (Djulbegovic & Guyatt, 2017). Therefore, when the patient population is heterogeneous, as it is with tick-borne diseases and associated illnesses, and patients require individualized care, regulatory decisions based primarily on CPG recommendations reflect an inherently flawed and unfair process for the clinician under investigation. The following excerpt describes one clinician's experience with an insurer:

"The first indication of trouble arrived unexpectedly, by registered letter. Reading in disbelief, I learned that an insurance company's credentialing committee had reviewed a quality-of-care case concerning my treatment of Lyme disease and, without ever speaking to me, determined that I 'provided inappropriate diagnosis and treatment of tick-borne illnesses.' The letter went on to inform me that I was terminated from the insurer's provider network. No details regarding the care concerns were provided.

Exclusion from the network would be a death blow to my practice, which provided the full range of primary care services in a small community where this particular insurer dominated the market....And so, I was forced to pick between the small group of marginalized, suffering Lyme disease patients that I had helped and my non-Lyme disease patients who made up the bulk of the practice. With a heavy heart, I chose the latter."

Traditional Economic Models

Traditional economic models are ill-suited to the care of PLD/CLD patients. The traditional model relies heavily on insurance compensation, but insurance compensation often does not match the time required to provide care. Thus, in the 2021 Clinician Survey, 74% of respondents indicated that they do not participate in insurance networks (Johnson & Maloney, 2022). This decision increases care costs for all patients and decreases access for patients who cannot afford the out-of-pocket expenses.

Medical Education-related Barriers

Improving health equity for patients with tick-borne diseases and associated illnesses requires a sufficient number of well-educated clinicians whom patients can readily access. Both the 2018 and 2020 Reports to Congress identified clinician knowledge gaps that

impact the diagnosis and management of patients with tick-borne diseases. The continued need for clinician education that promotes an increased awareness of tick-borne diseases and fosters a deeper understanding of these illnesses remains a significant concern.

Insufficient Instructional Time Devoted to Tick-Borne Diseases and Associated Illnesses in Medical Schools

The dramatic increase in medical knowledge presents an important challenge in tick-borne diseases. Medical knowledge, as measured by the volume of journal articles, has been increasing exponentially for over a decade, and this increase is likely to accelerate in the future. In contrast, instructional time in undergraduate medical education is essentially fixed. Thus, the need to cover more information in a fixed amount of time results in educational trade-offs. As such, tick-borne diseases compete with other high-impact, high-incidence topics such as diabetes and obesity for instructional time. Viewed in that light, it is understandable that limited classroom time is devoted to tick-borne diseases.

The implications of this educational framework profoundly affect clinicians' knowledge and hence their ability to care for patients with tick-borne diseases and associated illnesses. Clinicians generally leave school with limited knowledge of basic facts of tick-borne diseases and associated illnesses and with little exposure to the uncertainties mentioned above. As the complexity of tick-borne diseases becomes better known, clinicians must be able to incorporate additional information into their practice; thus, clinicians must be life-long learners (Ginzburg et al., 2021). Continuing medical education (CME) opportunities are part of the resources on which clinicians rely to remain life-long learners. Therefore, clinicians require access to high-quality CME courses and educational content that are designed to fill these educational voids. Although most clinicians prefer CME activities that are online, low or no-cost, and flexible (O'Brien Pott et al., 2021a, 2021b), only a few CME activities align with clinician preferences. Thus, clinicians often struggle to (a) identify many

disease presentations, (b) determine how to assess an individual's risk of disease based on history and exam, (c) recognize the limits of testing, and (d) individualize care. These struggles are reflected in the lived experiences of many patients who have found it difficult to obtain an accurate diagnosis and effective treatment when they initially sought medical care (Tick-Borne Disease Working Group, 2018).

Shortcomings in Government Educational Efforts

CDC and NIH, including the National Institute of Allergy and Infectious Diseases (NIAID) are leading medical authorities within HHS. The information on tick-borne diseases and associated illnesses provided by these agencies is extensively used by medical professional organizations, regulatory bodies, health insurers, researchers, medical educators, and providers. As such, CDC is ideally poised to take a lead role in providing comprehensive, factual, up-to-date information on Lyme disease on which clinicians can rely. However, the narrow scientific focus described both on the CDC CME modules and the CDC website on Lyme disease as well as on AGS and other tick-borne illnesses does not include what still remains unknown, what is uncertain, and what continues to be debated. Instead, the instructional materials present a simplified picture of the current state of the science. This not only limits the clinical utility of the information presented and constrains the ability of clinicians to make informed decisions regarding patient care, but also implies that the science is settled when it is not. These are missed opportunities to provide accurate, comprehensive knowledge to clinicians, not only regarding the underdiagnosis of tick-borne diseases and associated illnesses, but also the uncertainty regarding treatment.

On the CDC and NIAID websites and in the CDC training modules, information about PLD/CLD is incomplete. Because the scientific evidence is emerging and unsettled, this topic has generated considerable controversy, yet the content does not reflect the breadth of perspectives. CDC and NIAID do not distinguish between patients who are recent treatment failures and those who have been persistently ill for many years; yet these differences

in clinical status may affect the response to further antibiotic therapy. Both websites and the training modules omit significant facts regarding the four NIH-sponsored trials of antibiotic retreatment of persistent manifestations of Lyme disease following initial antibiotic therapy. Although discussions in the scientific literature regarding the findings from the retreatment trials are nuanced and remain subject to debate (Delong et al., 2012; Fallon et al., 2012; Klempner et al., 2013), not including the discussion altogether in favor of a generalized "retreatment doesn't work" approach can mislead clinicians on a topic that is critical to the care of patients with PLD/CLD.

Opportunities to Eliminate or Reduce Barriers

Improving access to high-quality care for patients with tick-borne diseases and associated illnesses requires a multi-pronged approach (Figure 10).

Improving the quality of CME programs on these infections and conditions is an important step. Clinicians must have an opportunity to gain a full understanding of the available evidence and the remaining scientific gaps. With respect to patients with PLD/CLD, clinicians must be made aware that divergent views exist on how to best diagnose and treat these individuals.

Given their broad reach, it is imperative that federal websites provide accurate, objective, and current evaluations of tick-borne disease research and information, including that relating to Lyme disease. Thus, a review of federal websites and training that include Lyme disease and other tick-borne disease content is warranted. The process for conducting this review must be transparent and inclusive with meaningful engagement of the following subject matter experts: (a) patients, caregivers, or patient
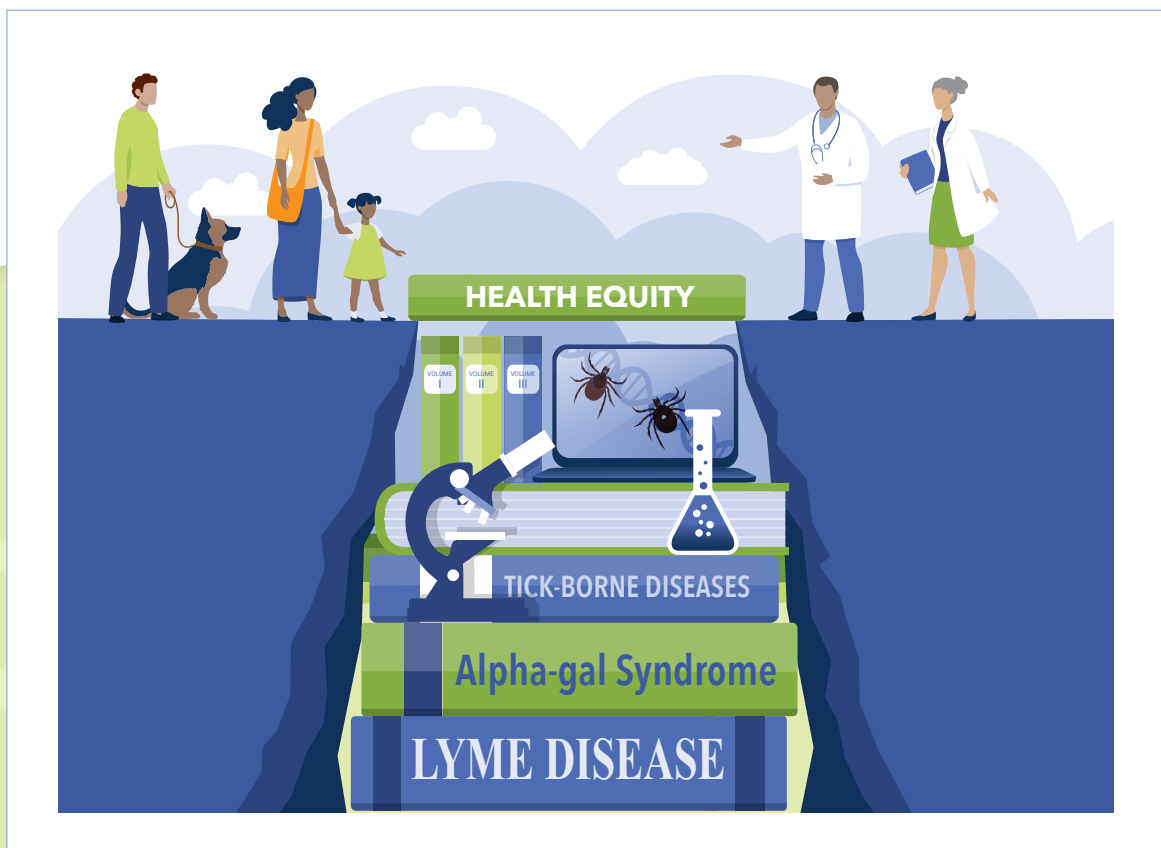

Figure 10. Bridging the access to care gap.

Jonathan Simoson

Jonathan became ill after a tick bite just a few weeks prior. He was diagnosed with Powassan virus disease after a series of medical visits during which the possibility of a tick-borne pathogen was raised. Jonathan was subsequently hospitalized with a high fever and was incommunicative while suffering from encephalitis. Jonathan's mother, Jamie, explained:

> **...what we're asking for is education.** We were adamant that he was bit by a tick. ... They didn't even—it's not even noted in any of their paperwork that he was [bitten] by a tick, even though we talked about it three times because there was no bull's-eye, the tick was not embedded, and the tick was not attached for more than, they're saying, 15 minutes, possibly, there was no chance that he could have gotten sick.

advocates who can meaningfully represent the acute and PLD/CLD perspectives and other tick-borne illnesses; (b) clinicians (including clinicians who treat patients with acute and PLD/CLD as well as clinicians who are subject matter experts in acute and PLD/CLD education); (c) research scientists with expertise/experience who represent diverse scientific perspectives on the full spectrum of Lyme disease; and (d) clinicians and researchers with expertise in the other tick-borne diseases and associated illnesses. All members of the committee should be involved with selecting priority areas for review, determining important outcomes that matter to patients, and conducting the review. The most effective short-term solution is to teach to the scientific uncertainty, that is, to identify where the uncertainty lies and how it impacts clinical diagnostic and therapeutic decisions, because failing to do so ultimately contributes to the health inequities faced by patients with tick-borne diseases and associated illnesses.

The continued use of telemedicine, which overcomes distance and travel-related cost barriers, will also improve access to care. A 2021 narrative review found that using telehealth was convenient and efficient and also decreased direct and indirect costs to the patient (travel cost and time) and health care service provider (staffing), lowered onsite health care resource utilization, improved physician recruitment and retention, improved access to care, and increased education and training of patients and health care professionals (Butzner & Cuffee, 2021).

Filling the scientific gaps related to tick-borne diseases and associated illnesses will ultimately improve access to care. However, given that they are research disadvantaged illnesses, increased federal funding is critically needed to expand research avenues through the use of innovative research approaches, including CBPR. CBPR approaches could aid in closing the research gap. CBPR enhances community capacity by supporting community participation in the research from which they will directly benefit, with community members treated as equals. This approach creates a collaborative atmosphere encompassing patients, academic researchers, clinicians, and industry that accelerates the pace

of research while building research capacity within the community and developing both trust and expertise among participants. Stephen Groft, former director of the National Center for Advancing Translational Sciences' Office of Rare Disease Research, fostered collaboration between patient registries, biorepositories, academic researchers, and clinicians. In Lyme disease, many of these pieces are already in place, including the MyLymeData patient registry, the Lyme Biobank (a project of the Bay Area Lyme Foundation), and the Columbia Clinical Trials Network. The addition of a community clinician network of providers who treat patients with persistent Lyme disease would further accelerate Lyme disease research.

Big Picture Summary

The limited access to quality health care and other health disparities experienced by patients with tick-borne diseases and associated illnesses results from the interaction of multiple structural and societal determinants of health. Identifying and changing the educational, research, and administrative policies, processes, and practices that result in barriers to receiving and providing care is essential to achieving health equity for these patients.

Chapter 4

Changing Dynamics of Tick Ecology, Personal Protection, and Control

Recommendations

The Working Group identified three recommendations to address the increasing threat and public health challenge of tick-borne diseases and associated illnesses in the United States. The lack of funding continues to severely limit the ability to address most of the goals and recommendations in the 2018 and 2020 reports. Currently very few tick control tools are available to residents, much less communities, and there is scant evidence that any tools reduce tick bites or human disease, even for tools proven effective in killing ticks.

Recommendation 4.1: Increase funding for research on tick ecology towards more effective tick and tick-borne disease surveillance and tick control. Tick ecology is an important part of the One Health concept that also includes people and companion animals.

Rationale

The primary drivers of tick populations, tick pathogen prevalence, and geographic expansion of ticks and tick-associated diseases and illnesses need to be clearly defined to ensure the *selection of appropriate and effective tick bite prevention and control* approaches (Eisen et al., 2012; Kilpatrick et al., 2017). Human-biting tick species are significantly expanding their geographic range; in addition, there is significant risk for importation, establishment, and expanded distribution of exotic ticks and their associated pathogens in the United States (Molaei et al., 2022). One recent example is the self-cloning

Asian longhorned tick (*Haemaphysalis longicornus*), native to East Asia and capable of transmitting a number of pathogens, including Rickettsia spp. Questions about primary drivers include (a) how do habitat diversity and forest fragmentation impact disease risk; (b) what rates of host infestation are required to maintain enzootic transmission; (c) how can outcomes of interventions on ticks or hosts be improved; (d) how does human behavior influence tick-borne disease risk; and (e) how can risk assessment methodology be improved. Although the primary drivers for establishment, growth, and expansion of tick populations are generally known, the details of how they impact different tick species, or other widely distributed tick species in different parts of its range, are less well understood.

Recommendation 4.2: Increase funding to develop, evaluate, and deploy tick bite prevention and tick control approaches and strategies. Minimize roadblocks and streamline the regulatory process for getting new tick bite prevention and tick control products to market.

Rationale

More evidence is needed on the effectiveness of existing integrated and individual strategies to reduce human tick bites and associated human tick-borne illness. Current research tends to focus on the evaluation of methodologies without a clear road to regulatory approval or commercialization. There is a long timeline from basic proof-of-concept research to field evaluations, to commercial development, to licensing and registration, and to availability to the

public. Continued support for the development of existing and novel strategies with a more effective commercialization process would enhance the ability of researchers and industry to get new tick bite prevention and tick control products to market.

Recommendation 4.3: Increase adoption and expand knowledge of tick bite prevention and tick control methods across all affected groups, including implementation of occupational standards for employees at high risk of tick-associated illnesses.

Rationale

A focus on occupational and high-risk activities for exposure to ticks is an important addition to previous findings. Risk factors such as occupation, lifestyle, and travel history are important pieces of information in a diagnostic workup for tick-borne diseases and associated illnesses. A tick species that becomes established in new regions has the potential to introduce new tick-borne pathogens for which it is a vector (Paules et al., 2018; Wikel, 2018, 2022). Physicians, veterinarians, public health workers, and the general public need to be made aware in a timely manner of these potential threats as they emerge in a new area. Knowing where ticks and tick-borne pathogens are present is foundational to understanding the health threats they pose and determining appropriate treatment. As noted by Eisen and Paddock (2020), "the prevention and diagnosis of [tick-borne diseases] depends greatly on an accurate understanding by the public and

healthcare providers of when and where persons are at risk for exposure to human-biting ticks and to the pathogens these ticks transmit." Workers in outdoor occupations have a high risk of tick exposure, and they and their employers should have access to the most current tick bite and tick-borne disease prevention tools available. Broad stakeholder engagement and enhanced education—developed with a health equity lens—are needed for health care providers and at-risk populations, including minority groups.

Background

Ticks and tick-borne pathogens are a persistent U.S. and global public health threat that is an increasing challenge because of (a) expanding geographic ranges of multiple tick species and the pathogens they harbor; (b) recent emergence of previously unrecognized tick-transmitted infectious agents; and (c) the complex climatic, environmental, and human interactions that influence tick abundance, the risk for tick-borne disease, and strategies for tick control (Dantas-Torres, 2015; Sonenshine, 2018; Tsao et al., 2021; Wikel, 2018). Among arthropod vectors, ticks transmit the greatest diversity of infectious agents to humans, livestock, and companion animals (Jongejan & Uilenberg, 2004). Within the United States, the majority of reported vector-borne human infections are attributed to ticks (Eisen & Eisen, 2018; Rosenberg et al., 2018) (Figure 11). Although Lyme disease is the most reported tick-borne disease in North

Majority of Reported Vector-Borne Diseases Are Spread by Ticks

Mosquito- or Flea-Borne Diseases (2.0–5.4%)

Other Tick-Borne Diseases[1] (27.0–30.7%)

Lyme Disease (66.7–67.9%)
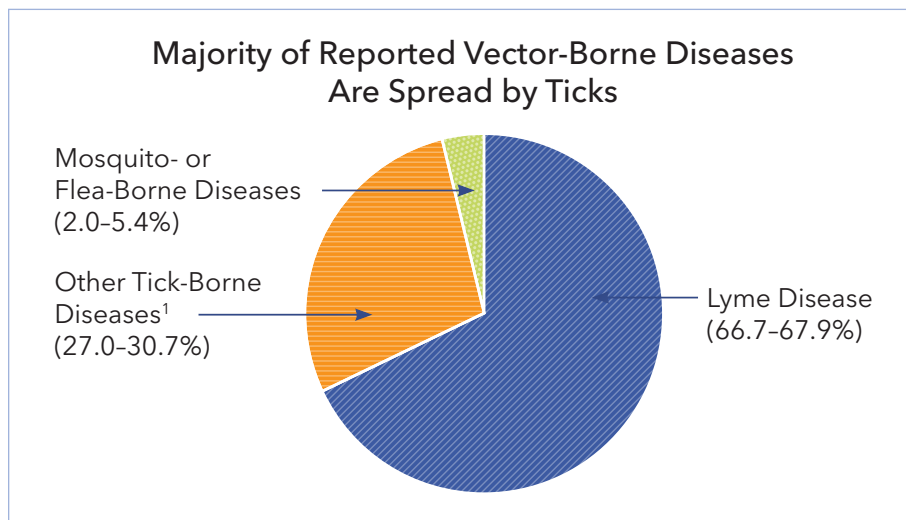
Figure 11. Cases of nationally notifiable vector-borne diseases in the United States, 2017–2019.

[1] The graphic does not include 34,256 positive diagnostic tests for alpha-gal, during 2010-2018. The lone star tick has been implicated as the primary cause for the development of Alpha-gal Syndrome, although other tick species may be involved.

Sources: Binder et al., 2021; CDC, 2020c.

America (Mead et al., 2018), the Centers for Disease Control and Prevention (CDC) recognize at least 18 tick-borne pathogens and medical conditions, such as Alpha-gal Syndrome ("red meat" or mammalian-derived product allergy) and tick paralysis, that cause human illness. This list does not include the many tick-associated pathogens or diseases solely associated with our livestock or companion animals. Exotic ticks and tick-borne diseases also pose a threat to the health of U.S. populations, as well as tourists, military personnel, and civilians living and working abroad. Although some of those diseases are not yet established in the United States, the recent rapid geographic spread of the invasive Asian longhorned tick in the United States illustrates the potential for the introduction of new tick species and tick-borne pathogens.

Tick-borne infectious diseases of humans are zoonoses (Eisen et al., 2017), which means they are maintained in non-human hosts. The movement or transport of wild and domestic host populations (e.g., migratory birds, exotic animals, and cattle), as well as the geographic and demographic expansion of ticks with their associated pathogens, are a major driver of tick and tick-borne pathogen emergence. The top five ixodid species recorded from humans in the United States are the blacklegged tick, the lone star tick, the American dog tick, the Western blacklegged tick, and the Rocky Mountain wood tick (Figure 12). Other ticks of increasing concern include the brown dog tick and the exotic Asian longhorned tick, but a total of 36 ixodid species and 13 argasid (soft tick) species are noted in the literature as able to infect humans (Eisen, 2022). Critical to reducing

U.S. tick distribution: 1. Blacklegged Tick; 2. Western Blacklegged Tick; 3. American Dog Tick; 4. Gulf Coast Tick; 5. Lone Star Tick; 6. Rocky Mountain Wood Tick; 7. Brown Dog Tick; and 8. Asian Longhorned Tick.
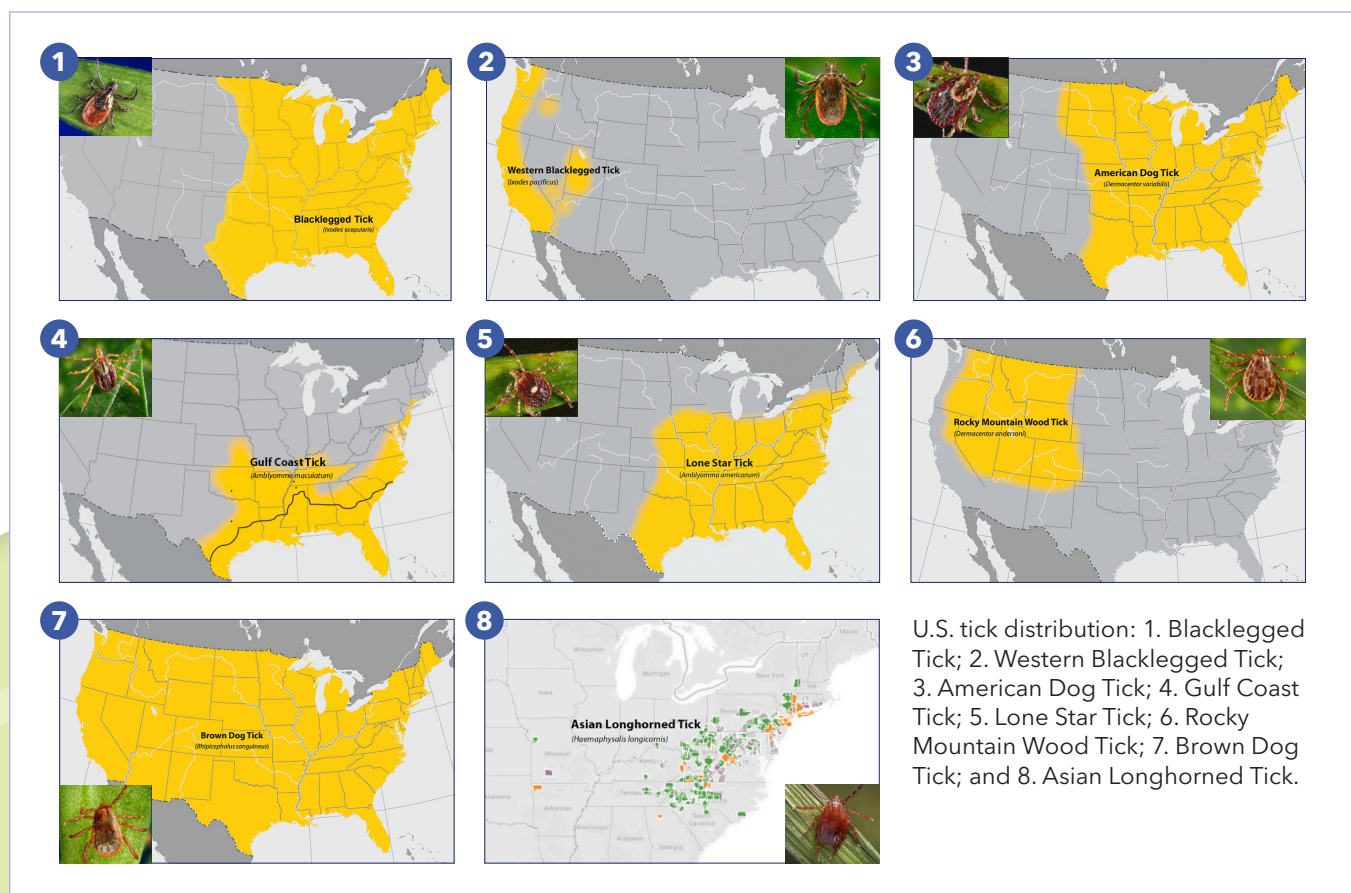
Figure 12. Ticks of major medical and veterinary importance in the United States.

Sources: Maps 1-2, 5-7: CDC, 2021h.
Map 4: Adapted from Sonenshine, 2018.
Map 8: Pennsylvania Department of Environmental Protection, 2022.
Photos: CDC.

the incidence of established and emerging tick-borne diseases is a required understanding of how ecological, environmental, and human social factors contribute to the increased risk of tick bites and tick-borne disease. Currently, there is little evidence for individual strategies or integrated tick management resulting in reduced human tick bites and human tick-borne illness.

Previous Work of the Tick-Borne Disease Working Group

The main objective of this chapter, and those on tick biology, ecology, and control in the 2018 and 2020 Tick-Borne Disease Working Group Reports to Congress, is to identify strategies to reduce human risk of tick bite and tick-associated illnesses. The objectives, recommendations, and many of the findings in those earlier report chapters—related to conducting tick surveillance, assessing current and developing novel tick control measures, validating integrated tick management strategies, measuring human outcomes, and increasing tick education and awareness—remain crucial and relevant. The increasing numbers and diversity of tick-borne infections in the United States, along with weak epidemiological evidence of the ability of existing personal protection measures and environmental tick control methods to prevent tick bites and disease, has increased calls for better surveillance and a national strategy to address vector-borne disease threats (Beard et al., 2019, 2021). The national strategy includes the following:

- the need for focused and area-wide integrated tick management programs;

- increased incentives for academia and industry to develop, test, and register new tick control technologies;

- updated strategies to address the increasingly more complex tick and disease threats occurring in a changing landscape; and

- expanded educational initiatives for both professionals and the public.

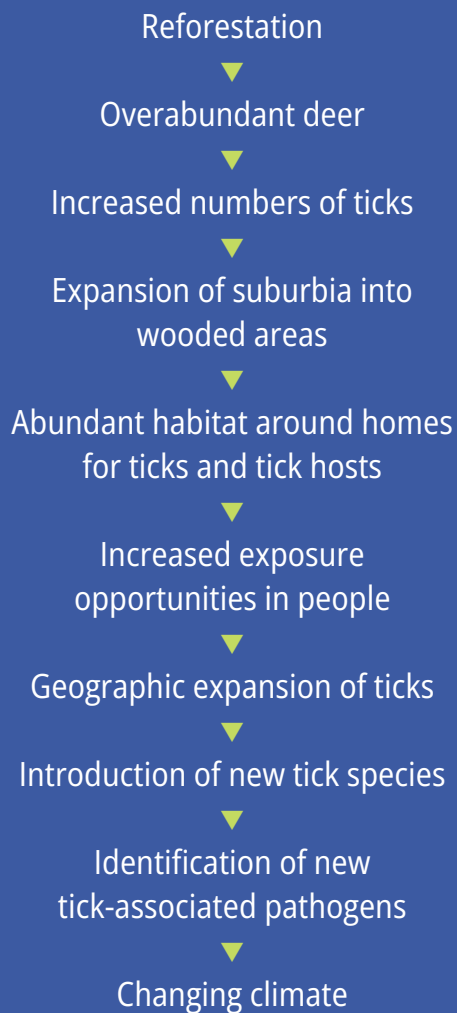While many challenges remain, the recommendations in the present and previous Reports to Congress outline the strategies, path, and support needed to advance these goals.

Major Challenges and Issues

Although the many primary drivers for emergence, establishment, growth, and expansion of tick populations are known, the details of how they impact different tick species, or a widely distributed tick species in different parts of its range, are less well understood (Eisen et al., 2012; Kilpatrick et al., 2017) (Inset, p. 39). Significant geographic range expansion of native tick species and risk for importation and establishment of exotic tick species and their associated pathogens are factors of increasing concern (Molaei et al., 2022). As vectors of Lyme disease spirochetes, blacklegged ticks (*Ixodes scapularis*) and western blacklegged ticks (*I. pacificus*) have been the focus of most research in the past several decades (reviewed by Eisen & Dolan, 2016; Mathisson et al., 2021; Stafford & Williams, 2017; Stafford et al., 2017; White & Gaff, 2018). Even for these extensively studied species, much remains to be learned (Eisen & Stafford, 2021; Tick-Borne Disease Working Group, 2020). Geographical differences have been observed for seasonal activity patterns of different life stages, questing behavior of larval and nymph life stages, and patterns of host use. These differences influence natural cycles of pathogen transmission as well as human risk of encountering questing ticks (Figure 13). The challenge is that research is needed not only for *I. scapularis* and *I. pacificus*, but also for a diversity of tick species, particularly the lone star tick (*Amblyomma americanum*) with its aggressive host-seeking behavior. Necessary research includes fundamental studies on the biology and ecology of ticks throughout their geographical ranges, to better understand local dynamics of tick population establishment and growth, and pathogen transmission potential.

Limited surveillance data, especially for emerging tick species, impacts the ability (a) to inform local public health messaging regarding when and where people are most at risk for bites by different tick species and

Drivers for Emergence of Tick-Borne Diseases

Reforestation
▼
Overabundant deer
▼
Increased numbers of ticks
▼
Expansion of suburbia into wooded areas
▼
Abundant habitat around homes for ticks and tick hosts
▼
Increased exposure opportunities in people
▼
Geographic expansion of ticks
▼
Introduction of new tick species
▼
Identification of new tick-associated pathogens
▼
Changing climate

life stages and (b) to model tick populations and pathogen transmission dynamics (Diuk-Wasser et al., 2012; Eisen & Paddock, 2020). Tick surveillance, whether documenting the expanding range of native ticks or intercepting invasive ticks at U.S. borders, is fragmented across different federal entities, state/local public health entities, the academic research community, and commercial tick identification and pathogen testing companies. Accurate tick identification is critical to early detection and effective action but is currently limited by (a) a small (and diminishing) cadre of trained tick taxonomists, (b) the current use of geography (local taxonomic keys) for morphological identification, and (c) the need to identify the species for each tick life stage, some of which may lack diagnostic characters. A correct identification is essential for clinicians and patients to determine tick disease risk. While classical taxonomy remains the main approach for tick identification, the use of alternative identification tools such as DNA, RNA, or protein analysis can also provide rapid, high throughput processing as well as the concurrent detection of tick-borne pathogens. However, accurate genetic determinations require accurate information in the genetic databases.

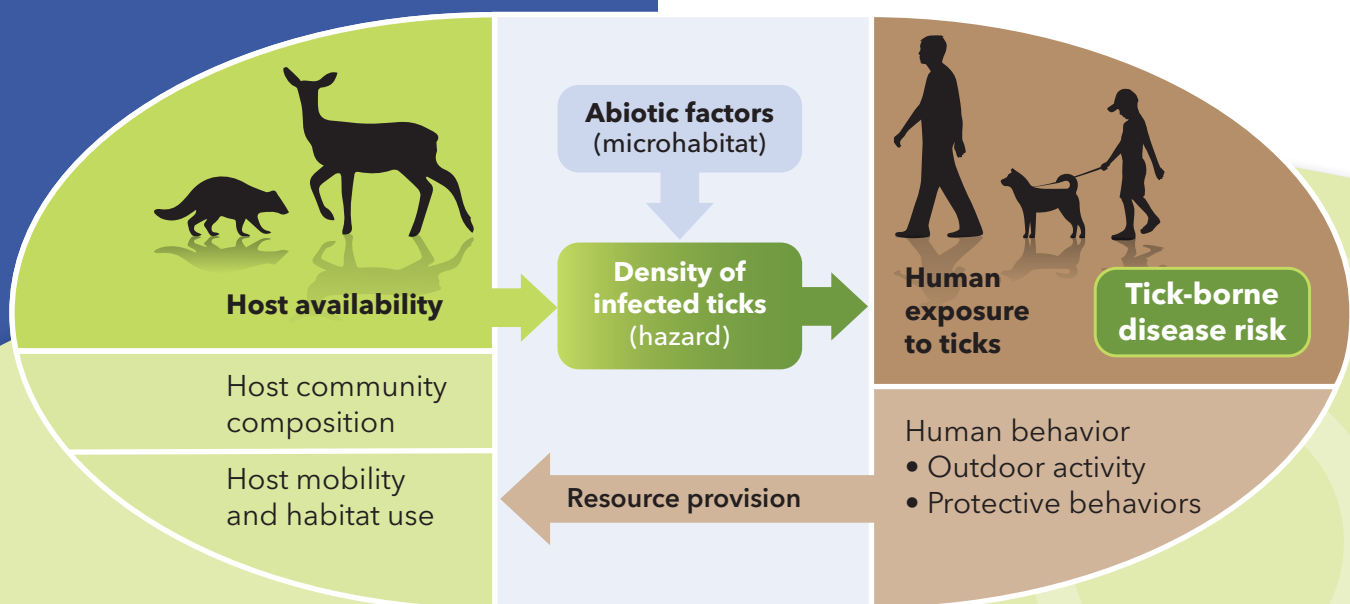Currently, evidence is lacking to show how environmental tick suppression methods reduce

Figure 13. Ecological and human interactions associated with risk of tick-borne disease.
Source: Adapted from Diuk-Wasser et al., 2021.

either human tick bites or tick-borne illness (Eisen & Stafford, 2021; Hinckley et al., 2016, 2021). There is a critical need for novel concepts and approaches in addition to evaluating the effectiveness of existing approaches to prevent tick bites and reduce tick-borne disease. The evidence base for tick suppression is strongest for broadcast of conventional synthetic acaricides, moderately strong for broadcast of natural product-based acaricides/biological control agents or acaricide treatment of rodents and deer, and weakest for hardscaping/xeriscaping and vegetation management. Existing strategies, including the application of acaricides, host-targeted methods, and integrated tick management studies have been shown effective in reducing the blacklegged and lone star tick abundance (Bloemer et al., 1990; Keesing et al., 2022; Stafford & Williams, 2017; Stafford et al., 2017; Williams et al., 2018). However, additional research is needed to determine how environmental tick suppression methods are to be optimally used, singly or in combination, to reduce human tick bites or tick-borne disease most effectively based on variable application schemes. Large-scale single or integrated programs have yet to document a significant impact in incidence for human tick-borne disease (Hinckley et al., 2016; Keesing & Ostfeld, 2018; Keesing et al., 2022). While the treatment or reduction in white-tailed deer has demonstrated some impact on human cases of Lyme disease with some caveats, there is a need for further evidence on the impact of human disease risk under more diverse ecological settings (Garnett et al., 2011; Kilpatrick et al., 2014; Kugeler et al., 2015). In suburban residential settings, the burden of tick control falls on residential property owners, who have the choice of doing it themselves or hiring pest control firms. Organized public health–related tick control is either lacking or poorly developed across the United States (Eisen, 2021; Piesman & Eisen, 2008); only 3% of 491 surveyed local operational vector (mainly mosquito) control programs or health departments engaged in any tick control activity (Roy, 2021). Additional research is needed to determine how environmental tick suppression methods are to be optimally used—singly, in combination, on a larger scale, or under

different climatic regimes—to most effectively reduce human tick bites or tick-borne disease based on variable application schemes and public acceptance. In addition to new materials for killing host-seeking ticks, methods targeting animal reservoir hosts (hosts carrying the pathogen; e.g., white-footed mouse) or tick reproductive hosts (major hosts for the female tick that amplify tick populations; e.g., white-tailed deer) are likely to be an essential component of integrated programs to reduce tick-borne diseases (Table 1). Ticks are increasingly the foci of genomics and functional genomics studies, and these technologies have significant potential to provide new insights for development of novel control approaches with greater target specificity.

Immunization of wild animals to prevent human and domestic animal disease is one of three vaccine deployment frameworks, the others being vaccination of humans and of domestic animals (Monath, 2013). The first approach focuses on vaccination of wildlife to disrupt arthropod vector transmission of infectious agents to humans. Oral vaccination is a favored and established method for control of diseases in wildlife that are transmissible to humans and domestic animals. Oral vaccination regimens, including reservoir-targeted vaccines and oral acaricide baits for wildlife reservoirs of tick-borne pathogens and for wildlife species that amplify tick populations, such as white-footed mice and white-tailed deer, are achievable objectives that have the potential to reduce infected tick populations (Ndawula, 2021; Richer et al., 2014; Stafford III et al., 2020; van Oosterwijk & Wikel, 2021). Using genomic approaches for tick control, the products of many newly discovered genes may be suitable targets for novel repellents, acaricides, growth regulators, anti-tick vaccines, and potential genetic manipulations that block tick feeding and vector competence. Advances in understanding the complex, dynamic interface of tick-host-pathogen interactions are linked to improving (a) genomic tools available for salivary gland transcriptomics and proteomics; (b) high throughput next generation sequencing; (c) gene silencing by RNA interference or CRISPR-Cas; and (d) a new embryo injection technique, which will facilitate

Table 1. Potential Advances to Improve Tick Control and Personal Protection

Personal Protection Measures	Killing Host-Seeking Ticks	Rodent-Targeted Approaches	Deer-Targeted Approaches
Novel and extended release repellent/ soap/lotion	Plant-based acaricides (e.g., nootkatone)	Oral Lyme disease vaccine	Oral parasiticide
	Acaricide with semiochemicals	Oral antibiotic bait	Oral tick growth regulator
	Mineral-based acaricides	Oral tick growth regulator	Novel, topical acaricide applications
		Oral parasiticide	Anti-tick vaccine for deer

Note: Treatment for humans is covered in in Chapter 7: Disease Prevention and Treatment.

Source: The Connecticut Agricultural Experiment Station.

an understanding of the sequential patterns of early embryological events and the genetic manipulation of ticks (Nuss et al., 2021; Wikel, 2018). Although transgenic tick research is in its infancy, the potential benefits of transgenic tick basic research are significant, and sustained funding for this research area is encouraged. Nevertheless, determining the specific biological activities of individual saliva and other tick tissue molecules for development of anti-tick vaccines remains a challenge.

Industry has three broad roles in the field of tick control and tick-bite prevention: (a) production of already marketed products to kill or repel ticks; (b) development and commercialization of new acaricide or repellent active ingredients and formulations, as well as other novel products such as wildlife-targeted oral baits and anti-tick vaccines; and (c) provision of services by pest management professionals (e.g., local pest control companies or franchises). Basic research tends to focus on the development of new methodologies without a clear path to regulatory approval or commercialization, and there are key knowledge gaps. Given the extensive timeline from basic proof-of-concept research to field evaluations, and subsequently to commercial development and availability to the public, there is a need for

continued support for evaluation and development of existing and novel strategies. Implementation of novel technologies requires long-term research followed by commercial product development with associated costs, patent or licensing issues, registration approvals, marketing, and actual acceptance and use by the public or pest management professionals (Graf et al., 2004). Supporting critical partnerships throughout the development process will expedite the progress of intervention strategies, including commercialization and marketing of the most promising new and/or existing technologies to reach the widest possible segments of the U.S. population at risk of Lyme disease and other tick-borne illnesses.

The product development pipeline from early research through commercialization presents challenges that can derail even the most promising tick bite prevention and tick control technologies, particularly in the transition from basic and applied research to product development and scale-up (this funding gap is sometimes referred to as the "valley of death") (Beard et al., 2009; Ford et al., 2007; Hudson & Khazragui, 2013) (Figure 14). This process takes approximately 10-15 years from proof of concept in the laboratory to commercialization, often due to funding gaps in the areas of prototype development,

testing and evaluation, and regulatory requirements. A more effective pathway is critically needed to develop, register, and commercialize tick bite prevention and tick control products.

Lyme disease patients, and likely patients with other tick-borne diseases and illnesses, are often unaware of a tick bite prior to symptoms onset (Eisen & Eisen, 2016). In a survey of Alpha-gal Syndrome patients, 20% of participants did not remember having a tick bite (Platt & Merritt, 2022). Thus, novel products capable of killing undetected feeding ticks could be of great value to complement existing personal protection measures. A novel compelling approach to achieve this, for example, would be a skin lotion, shower soap, or shampoo containing an active ingredient that is safe to apply to human skin and has acaricidal properties, such as nootkatone. Nootkatone, from Alaskan yellow cedar or grapefruit essential oil, has been shown to be both repellent and toxic to at least four tick species in a series of federally funded laboratory and field studies published from 1997 to 2012. Only recently, however, are nootkatone-based products targeting mosquitoes and ticks being

developed under license from CDC. Nootkatone was registered by the U.S. Environmental Protection Agency as a biopesticide in 2020.

Implementation of novel technologies requires long-term research, demonstration of efficacy, and commercial product development and includes associated costs, patent or licensing issues, registration approvals, marketing, and actual acceptance and use by the public or pest management professionals. With a more effective process in place for bringing new tick bite prevention and tick control products to market, promising new products could emerge on timelines far shorter than we have experienced over the past decades. One approach to enhancing development could be to expand the purview of the Biomedical Advanced Research and Development Authority (BARDA) to include vector-borne diseases, and to provide BARDA with funding to work with industry to bring a new focus on getting tick bite prevention and tick control products to market. Collaboration on development of new products combining patented, individual technologies such as acaricides,
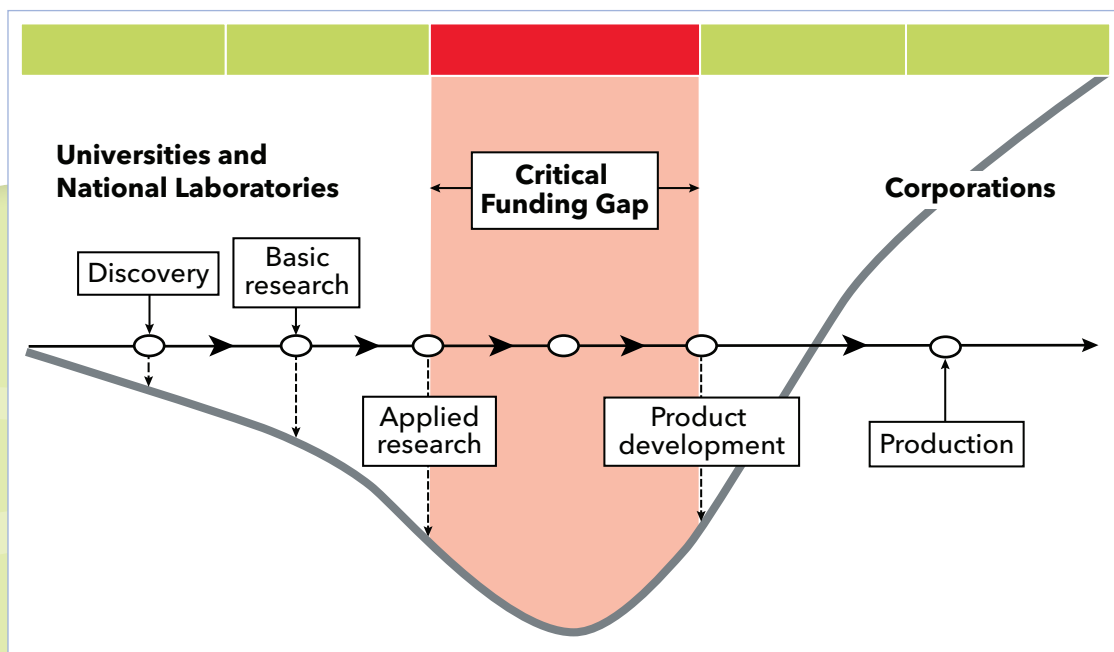

Figure 14. Research and development funding gap for tick control and personal protection products.

Sources: Based on the concept in Beard et al., 2009; Ford et al., 2007; Hudson & Khazragui, 2013.

reservoir-targeted vaccines, and different delivery systems to synergize existing technologies should be encouraged. Regulatory obstacles for product concepts involve many different federal regulatory agencies, depending on the product, and required registrations and approvals should be streamlined.

Specific circumstances that underlie tick encounters with people are not well understood (Eisen, 2021; Eisen & Eisen, 2016; Eisen & Stafford, 2021; Eisen et al., 2012). Up to 75% of tick bites in Connecticut and the Northeast are estimated to occur in residential settings where forested tick and host habitat is present (Mead et al., 2018; Stafford et al., 2017). Around 20% of tick bites are associated with activities away from the home, likely through neighborhood and recreational activities such as walking the dog, playing near edges of school grounds, and hiking and camping at parks and state forests, or through outdoor occupational activities (Fischhoff et al., 2019; Hahn et al., 2018). Outdoor occupational workers have a particularly high risk of tick exposure (Piacentino & Schwartz, 2002; Schwartz & Goldstein, 1989; Schwartz et al., 1994). Non-chemical personal protection measures (e.g., wearing untreated protective clothing and conducting tick checks) can be more effective than applying skin repellents. Unfortunately, workers and their employers in many states lack access to the most current tick bite and tick-borne disease prevention information and tools available. Although there are existing information resources for how to prevent tick bites, a better understanding of why some members of the public choose to not protect themselves and their families against tick bites is needed to generate impactful messages to increase the use of tick bite prevention and tick control measures, particularly in underserved communities.

Although the tick species involved is the first and major risk factor for most tick-associated illnesses, occupational, lifestyle risk factors, and travel history are important factors in evaluating tick-borne disease risk upon tick bite. To expand knowledge and increase adoption of tick bite prevention and tick control methods across all affected groups, occupational standards for employees at high risk

of tick-borne diseases need to be implemented with additional broad stakeholder engagement and training needed for educators and at-risk populations, including minority groups.

Long-term costs of a tick-borne illness can be high and infection with some pathogens potentially life threatening (Zhang et al., 2006)—a potential liability for an employer. Although prevention information and recommendations are available from the National Institute of Occupational Safety and Health and many other sources, the Occupational Safety and Health Administration should have national workplace hazard assessment requirements or standards for employees in outdoor workplaces to address exposure to ticks and tick-borne pathogens. Implementing a robust employer tick disease and tick-bite prevention program—including training, policies and procedures, habitat awareness, high versus low tick density areas, personal protective equipment, and the use of the wide variety of repellants available—could significantly reduce employee exposure and potential employer liability, and convey confidence that protective measures are being taken.

Previous tick-borne disease prevention educational efforts in the United States have shown some increased knowledge and use of personal protection measures against tick bites. However, in a national HealthStyles survey (Hook et al., 2015), a majority of respondents (51.2%) did not routinely utilize personal protections against tick bites, and few (10.7%) reported using yard pesticides to reduce ticks, despite 21% of respondents reporting that a household member was bitten by a tick the previous year. There are likely several barriers toward increased adoption of prevention measures despite previous education efforts because it is not well understood how prevention messages can increase use of personal prevention measures and whether the measures are used effectively (e.g., how often a protective action is taken, which parts of the body are protected, and how tick checks are conducted). Needed are additional studies to determine which types of messages are most effective in leading to behavioral change, including messaging that targets

underserved communities and different types of risk groups. Development of repellent formulations or preventatives that are easy to use and acceptable to the public could also increase usage.

Big Picture Summary

The number and diversity of tick-borne infections in the United States have significantly increased, and several native and recently introduced exotic tick species are expanding their ranges in the United States, placing new human populations at risk for tick-borne pathogens. There is scant evidence that any current tick bite prevention and tick control tools reduce tick bites or human disease, even for tools proven effective in killing ticks. Although progress has been made to address the surveillance, ecology, and control recommendations in the 2018 and 2020 Reports to Congress, gaps remain. The Working Group recommendations in this chapter address continued gaps in our knowledge of (a) the efficacy of existing bite and control strategies to prevent human disease and development of novel tick control methodologies; (b) the changing dynamics of tick expansion in distribution, their ecology, and associated tick-borne disease risks to *select appropriate and effective tick bite prevention and control approaches*, which includes the environmental, social, and occupational issues influencing adoption and use, or lack thereof, of measures to reduce tick bites and pathogen exposure; and (c) the barriers that exist in the development and commercialization of tick bite prevention and tick control products. The increasing numbers and diversity of ticks and tick-borne infections in the United States call for increased support for the Working Group's recommendations and a national strategy to better understand and address the threat of tick-borne diseases and associated illnesses.

Chapter 5
Clinical Presentation and Pathogenesis

Recommendations

The following recommendations were developed by the co-chairs based on the six sections presented in the Clinical Presentation and Pathogenesis Subcommittee Report. These recommendations were approved in totality by the full Tick-Borne Disease Working Group at its April 2022 meeting.

Recommendation 5.1: Support additional research on the mechanisms of pathogenesis of tick-borne disease, with a particular focus on central nervous system infection (including neuropsychiatric illness and neuropathic injury), persistent symptoms, allergy (Alpha-gal Syndrome), immunity, autoimmunity, pregnancy, and adverse fetal outcomes.

Rationale

The underlying basis for persistent symptoms related to tick-borne or tick bite–associated disease is often poorly understood. Defining the precise mechanisms of pathogenesis is critical to ensure safe and effective treatment options for persons who suffer from these illnesses.

Recommendation 5.2: Provide funding to support research investigating the prevalence of undetected tick-borne illness among subgroups of the population who may have multi-systemic chronic conditions (e.g., mental illness, musculoskeletal diseases, etc.) and who have been inadequately medically evaluated, including individuals in psychiatric facilities, prisons, homeless shelters, other populations experiencing health disparities or disabilities.

Rationale

The full spectrum of clinical presentation for various tick-borne diseases is often poorly understood, especially for some of the less common diseases and particularly in persons and communities that are medically underserved.

Recommendation 5.3: Require labeling of foods, products, beverages (including alcohol), cosmetics, and pharmaceuticals that contain non-primate mammalian ingredients (active or inactive) and update the FDA's Food Safety Modernization Act to incorporate Alpha-gal Syndrome (AGS) awareness training into the FDA's "Retail Food Industry/Regulatory Assistance and Training" Program.

Rationale

People who develop AGS may develop symptoms upon exposure to red meat and various mammalian products. In addition, many AGS sufferers must worry about medications, products, and cross-contamination, which limits their daily lives.

Recommendation 5.4: Provide funding for studies, particularly prospective studies, that evaluate clinical similarities, mechanisms of pathogenesis, and common etiologies for long COVID and other infection-associated chronic illnesses, with tick-associated chronic illness and/or persistent symptoms associated with tick-borne diseases.

Rationale

Many patients who have experienced SARS CoV-2 infection report persistent symptoms, often including fatigue, post-exertional malaise, and cognitive impairment, among others. Given the array of overlapping symptoms, studies regarding the clinical similarities and common etiologies for long COVID and Lyme disease–associated chronic illness may provide insights into improved clinical management strategies.

Recommendation 5.5: Develop and maintain comprehensive biospecimen repositories (e.g., whole blood, sera, cerebrospinal fluid, maternal and fetal tissues and fluids, and autopsy specimens) for use in developing and/or improving diagnostic assays, both direct and indirect, and for research into transmission and pathogenesis, for broad applications including early diagnosis, distinction of current versus past infection, and for use in pregnancy and fetal outcome applications.

Rationale

A comprehensive biospecimen repository will provide a significant resource not only for developing improved diagnostic tests but also for the understanding of underlying mechanisms of pathogenesis and disease process, which is critical to developing improved therapeutics.

Background

Tick-borne diseases account for significant morbidity and mortality each year in the United States. Recent studies, based on insurance claims data, estimate that more than 476,000 Lyme disease cases are diagnosed and treated each year (Kugeler et al., 2021). In addition to reported cases, each year deaths occur, primarily from Rocky Mountain spotted fever, Powassan virus encephalitis, and Lyme disease carditis (CDC, 2021d, 2021e, 2022b). In areas where tick-borne diseases are common, patients who present with classic symptoms often receive prompt diagnosis and effective treatment, leading to good clinical outcomes. Unfortunately, symptoms of tick-borne diseases can be missed, and if ineffectively treated or left untreated, disease can progress to more serious illness with persistent and difficult-to-treat symptoms, and even death. Consequently, early and accurate diagnosis and treatment are critical for successful clinical outcomes.

Tick-borne diseases are increasing in the United States, both in annual case numbers and in geographic distribution (Beard et al., 2021). In addition to tick-borne infectious disease, there are emerging tick bite–associated conditions such as Galactose-alpha-1,3-galactose (Alpha-gal) Syndrome (AGS), which is triggered in the United States by the bite of the lone star tick, Amblyomma americanum. Recent studies indicate increasing trends in diagnosed cases in the United States, with the largest numbers of cases being reported across the central belt of the country, where the lone star tick is very common and frequently bites people (Binder et al., 2021).

As increasing numbers of people are at risk for tick-borne diseases, particularly in areas where these illnesses may not have been previously established. Prompt action must be taken to educate the public and health care community about changing patterns of risk. Health care providers must be equipped with state-of-the-science information on tick-borne diseases in order to provide accurate and timely diagnosis and treatment, thus minimizing the risk of more serious outcomes, including death. This information includes local risk of infection, range of clinical presentations, appropriate diagnostic tests and criteria, and safe and effective treatment options.

This chapter examines the major challenges and priority needs associated with clinical presentation and pathogenesis of tick-borne illnesses in the United States, specifically in the following topic areas:

- mechanisms of pathogenesis including autoimmunity, latency, persistence, and reemergence
- mental health
- neurologic and neuropsychiatric manifestations
- Alpha-gal Syndrome
- pregnancy and congenital infection

- lessons to be learned from long COVID

- health equity

Major Challenges and Issues

Mechanisms of Pathogenesis Including Autoimmunity, Latency, Persistence, and Reemergence

Several tick-borne disease pathogens have been newly recognized or distinguished, and the full spectrum of clinical presentation is incompletely understood. Symptoms can overlap with other illnesses, and to further complicate matters, co-infection with more than one tick-borne pathogen is not uncommon. Complications arising from tick bites, such as AGS, are also increasingly recognized (Commins, 2020). Thus, new research is needed to define the clinical presentation and mechanisms of pathogenesis for these diverse tick-borne pathogens that can infect humans. Defining mechanisms of pathogenesis is critical because it opens avenues for therapy. For example, if severe initial infection leads to persistent symptoms, then early treatment and vaccination strategies aimed at preventing severe and/or disseminated disease are likely to be effective at reducing persistent symptoms. Alternatively, if autoimmunity plays a role, then immune modulating therapies may be able to ameliorate disease course.

Neuropsychiatric Lyme Disease and Mental Health Issues

Although neuropsychiatric presentations of Lyme disease have been reported for more than three decades in the medical literature, rarely are the neuropsychiatric manifestations and mental health needs of Lyme disease described in medical textbooks or on government websites (Fallon & Nields, 1994; Kohler, 1990; Pachner, 1988). Lack of acknowledgement of this aspect of Lyme disease has led to delayed diagnosis and treatment, and in some cases severe long-term morbidity or, rarely, death due to suicide. These disparities are due, in part, to the reliance by clinicians on objective clinical signs described in the case definition for Lyme

disease (e.g., erythema migrans, facial palsy, arthritis), resulting in a skewed knowledge base that does not include atypical presentations (Perea et al., 2020).

Research into neuropsychiatric manifestations of Lyme disease has been largely confined to cognitive problems and depression, at the expense of other reported sequelae including anxiety, sleep disorders, psychosis, and sensory hyperacuities (Bransfield, 2018). In addition, issues related to methodological limitations such as small sample size, use of unvalidated measures, use of poorly specified criteria for the diagnosis of Lyme borreliosis, ascertainment bias, lack of an appropriate control group, reliance on clinical samples, lack of control for confounding variables, and lack of cross-sectional study designs have all played a role in perpetuating knowledge gaps and likely underdiagnosis of these conditions.

Overcoming these methodological limitations has proven difficult for several reasons (e.g., lack of reliable diagnostics); however, two recent, large nationwide cohort studies using Danish registry data have endeavored to shore up the gap in the evidence base (Fallon et al., 2021; Tetens et al., 2021). Both retrospective cohort studies investigated the temporal association of Lyme disease diagnosis and subsequent mental health diagnoses as well as associated outcomes, including rates of psychiatric medication prescriptions in the year following neuroborreliosis diagnosis, increased risk of affective disorder, suicidal behavior, or death by suicide. While causation could not be concluded, the presence of both a dose-response relationship and a temporal relationship to the occurrence of mental disorders was found, increasing the likelihood of a causal relationship between Lyme borreliosis and mental disorders.

Early localized Lyme disease generally does not have significant psychiatric features. Among patients who have been diagnosed with Lyme disease at any stage, however, up to 30% of patients report persistent symptoms despite antibiotic treatment for Lyme disease, depending on the study. In patients with Lyme disease–associated chronic illness, cognitive and psychiatric features can be prominent and
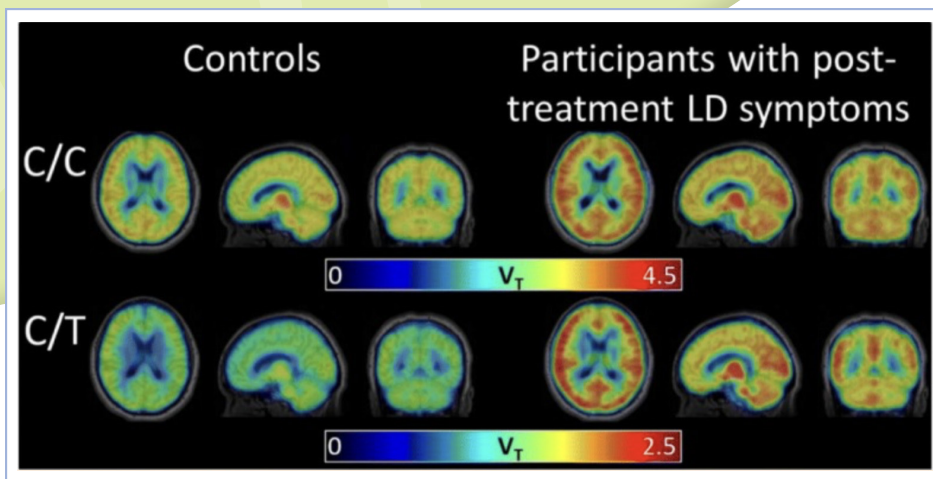
Figure 15. Positron emission tomography scans of brains of persons with and without post-treatment Lyme disease syndrome.

Source: Coughlin et al., 2018.

States. Both tick species are expanding their territory, and the reported cases of AGS are expanding as well (Binder et al., 2021; Platts-Mills et al., 2018).

The most common symptoms associated with AGS are gastrointestinal, integumentary (skin), and respiratory; however, recent research documents symptoms that range across all body systems (Table 2) and that vary from mild (e.g., rash, occasional headache, fatigue) to fatal (e.g., anaphylaxis, suicide from depression) (Platt & Merritt, 2022). Symptoms of food allergies differ significantly, depending on the immune mechanism involved and the affected target organ (Anvari et al., 2019). Severe symptoms include shortness of breath, wheezing, and repetitive cough. Blood pressure may decrease, but in a subset of patients with AGS, their blood pressure increases during a reaction (Platt & Merritt, 2022). Some people with AGS are extremely sensitive and report dizziness and even loss of consciousness with minimal exposure. Neurologic symptoms include a feeling something bad is about to happen, anxiety, and confusion. Urticaria or hives are red, raised rashes that itch, but some patients with AGS report burning with the rash. Others report a feeling of internal itching. Gut symptoms include acute stomach or intestinal cramping and pain, nausea, vomiting, and severe diarrhea. Not everyone with AGS has a life-threatening reaction. The symptoms of AGS can be immediate or more commonly up to 3-8 hours after eating red meat or mammal ingredients such as "gummy bears and capsules (gelatin), medications (for example, heparin and thyroid hormone), bioprosthetics (for example, porcine heart valves), surgical mesh, select vaccines, and unlabeled 'natural flavorings' in countless foods" (Commins, 2016).

Public commenters often refer to the fear and frustration associated with AGS. Living with AGS extends far beyond simply avoiding the consumption of red meat. Many people must worry about

disabling. Although suicide after diagnosis with Lyme disease is not common and the absolute risk is low, the rate in one of the Danish studies was increased by 75% among those with a hospital-based diagnosis of Lyme disease (Fallon et al., 2021). The period of greatest risk for mental disorders is the first year after hospital-based diagnosis, but the risk remains elevated for several years. The literature therefore supports the need for an increased recognition that Lyme disease can impact mental health and potentially contribute to suicide. Resources should be allocated for continued research into the mechanisms of pathogenesis (Recommendation 5.1), and to characterize the prevalence of tick-borne illness in persons with mental health diagnoses (Recommendation 5.2). Clinical care delivery should be optimized at the point of diagnosis to prioritize mental health support and treatment (Recommendation 5.2).

Clinical Presentation and Pathogenesis of Allergy to Galactose-alpha-1,3-galactose (Alpha-gal Syndrome)

In the United States, the lone star tick is associated with AGS; however, researchers now know that the alpha-gal carbohydrate also exists in the black-legged tick (*Ixodes scapularis*) (Crispell et al., 2019). Although *Ixodes* species have been associated with development of AGS in European patients, researchers have yet to explore the link in the United

Table 2. Alpha-gal Syndrome Patient-Reported Symptoms by Body System

Top Five Reported Systems/Symptoms:
DERMATOLOGICAL (skin): itching, flushing, hives/welts/urticaria, rash, hot/dry skin, red/itchy/watery eyes, swelling/angioedema
GASTROINTESTINAL: stomach pain/cramps, diarrhea, bloating, nausea, difficulty swallowing, tongue swelling/throat tightness, reflux
RESPIRATORY: trouble breathing/shortness of breath, wheezing, chest tightening/pain, itchy throat/ear canal, congestion, hoarse voice, coughing, anaphylaxis
CARDIOVASCULAR: lightheadedness/dizziness, rapid heartbeat, low blood pressure, irregular heart rate, weak pulse, low blood pressure
EMOTIONAL/BEHAVIORAL: anxiety, fatigue, headache/migraine, irritability, withdrawal from social/recreational activities, sleep disturbances, memory recall, panic, confusion, depression
Less Common But Also Reported Systems/Symptoms:
GENITOURINARY: urine difficulty, irregular/heavy menstrual flow, abdominal cramping, swelling/pain, reaction to bodily fluids
MOTOR (muscle): arm/leg weakness, clawing of toes, muscle cramping
NERVOUS (reflexes): fainting/loss of consciousness, abnormal sweating, weight change; tingling in mouth and extremities

Sources: Binder et al., 2022; Commins, 2020; Platt & Merritt, 2022.

medications, products, and cross-contamination, which limits their daily lives. In a recent survey, the five most common reactants were beef, pork, dairy, gelatin (usually in medications), and personal care products. While 25% of survey respondents experienced reactions 4-6 hours after exposure, 7% indicated reactions within 0-5 minutes. Exposure routes included ingestion, topical, and inhalation. Approximately 25% of respondents continue to react once or more per month after diagnosis. The top autonomic (neurologic) symptoms include abnormal sweating and fainting. Greater than 60% reported

anxiety along with a range of other mental health impacts (Platt & Merritt, 2022).

The pathogenesis of Alpha-gal reactions involves being sensitized to Alpha-gal, which causes the immune system to respond upon subsequent exposures to the allergen. In a 2022 article, Carson et al. described the proposed immune mechanism for developing AGS. During feeding, ticks introduce Alpha-gal in their saliva, potentially along with disease-causing bacteria and other substances that may alter the host immune response. Tick feeding may trigger the production of chemicals (cytokines) that further promote an allergic response. The immune response to Alpha-gal may convert the antibody-producing cells (B cells) in some people to switch to produce IgE, the allergy antibody.

Many patients indicate that they are not getting better despite months and even years of avoiding red meat and other mammal-derived ingredients. Other patients experience a period of latency followed by a return of symptoms after a new tick bite. Researchers have hypothesized that the allergic response to Alpha-gal may wane for some patients after several years; alternatively, there may be a state of "remission" given that additional tick bites can cause the allergy to recur (Commins, 2016; Commins et al., 2011; Khoury et al., 2018). For most patients, AGS appears to be a permanent condition.

Pregnancy and Lyme Disease

Lyme disease and pregnancy is an issue of special concern and importance given that both mother and baby are at a particularly sensitive time for health and development. The Lyme disease bacteria, *B. burgdorferi*, can be transmitted vertically, from mother, across the placenta, to offspring. This alternate mode of transmission, albeit considered rare in humans, is acknowledged by the Centers for Disease Control and Prevention (CDC, 2020b), the National Institutes of Health (2008), and Health Canada (Government of Canada, 2022). CDC currently estimates that 476,000 people are infected with Lyme disease each year in the United States (CDC, 2022a); however, it is currently unknown what

proportion of those diagnoses may occur in pregnant women and to what extent their pregnancy or developing fetus may be affected.

Limited research into this alternate mode of transmission in the past 25 years has resulted in significant data gaps, as well as a lack of clinical guidance and resources for health care providers. Impacted patient populations often struggle to access appropriate diagnosis, treatment, and care (Gaudet et al., 2019). Given the lack of high-quality, reproducible clinical and epidemiologic research on this topic, a standardized definition for congenital Lyme infection has not been established.

Despite previous research into Lyme disease and pregnancy involving animals and humans, several questions regarding occurrence and pathogenesis are yet to be answered. Past studies have been limited by generalizability issues, small sample sizes, inappropriate or no control groups, and limited laboratory evidence. Neither a causal association between gestational Lyme disease and specific adverse pregnancy outcomes nor a homogeneous congenital syndrome in exposed infants has been identified (Waddell et al., 2018). However, in many larger studies, *B. burgdorferi*–specific direct detection methodologies were not utilized to test exposed infants, placentas, products of conception, and/or autopsy specimens, resulting in lack of data to assess or determine a possible teratogenic effect or causal association.

Significant data gaps remain regarding how Lyme disease can impact pregnancy. There are questions about diagnostic sensitivity and effective treatment approaches in both mother and baby. Very little information exists on the potential for long-term health impacts of babies born to mothers with gestational Lyme disease. There is a need for better education of clinical communities and dedicated funding for research in this area.

In the 2020 Report to Congress, the Working Group considered the issue of maternal-fetal transmission of Lyme disease and congenital Lyme disease. The committee recommended that funding be provided for a registry and for more studies to determine the extent of maternal-fetal transmission of Lyme disease and of any congenital Lyme disease (Tick-Borne Disease Working Group, 2020, Recommendation 8.3). Since that time, CDC has begun efforts to understand the incidence and impact of Lyme disease during pregnancy. However, much remains to be investigated to clarify the occurrence of congenital infection and the pathogenesis associated with *B. burgdorferi* infection during pregnancy. Significant information could be gained from prospective epidemiologic studies (Recommendation 5.1).

The development of evidence-based interim clinical guidelines for Lyme disease in pregnancy are needed and could provide health care practitioners with resources and guidance in several important areas. These include (a) clinical evaluation and treatment of Lyme disease in pregnant persons; (b) evaluation of the fetus in pregnant persons with a Lyme disease diagnosis during pregnancy; (c) clinical evaluation and testing of infants born to persons diagnosed with Lyme disease during pregnancy; (d) recommended long-term follow-up for infants with

possible congenital Lyme disease infection; and (e) recommendations for histological examination/testing of placenta, umbilical cord, and/or products of conception or other autopsy samples. All of these guidelines could be updated with the emergence of new research or clinical findings.

Detailed clinical investigation and research collaboration that is aligned with patient-centric study design (Largent et al., 2018) will better define appropriate diagnostics and therapeutics, as well as inform clinical education and management of both the exposed mother and baby, ultimately providing much needed medical care, support, and hope for impacted families. It will also provide more clarity around the incidence, clinical spectrum, and potential long-term health consequences of infants exposed to Lyme disease in utero.

Clinical Comparisons of Long COVID and Lyme Disease to Elucidate Mechanisms of Disease

Many patients who have experienced a SARS CoV-2 infection report persistent symptoms that are highly debilitating and of unclear etiopathogenesis, referred to here as long COVID. Longitudinal studies published to date have suggested a range of 7-22% of confirmed COVID-19 patients continue to have symptoms past 28 days (Chevinsky et al., 2021; Sudre et al., 2021; Wanga et al., 2021). These symptoms include fatigue, post-exertional malaise, and cognitive impairment, among others. One prospective study evaluated a cohort of adults hospitalized due to COVID-19 and compared long-term outcomes to controls (non-COVID-19 participants) matched on age, sex, and comorbidities (Huang et al., 2021). At 12 months, COVID-19 survivors had more symptoms, including problems with mobility, pain, or anxiety or depression, compared with controls. Moreover, the odds of specific long COVID symptoms (e.g., fatigue or muscle weakness, anxiety or depression, and pulmonary function impairment) were higher among women than men.

Long COVID is generally thought to be caused by either long-term damage to tissues (e.g., lung, brain, and heart) or pathological inflammation (e.g., from viral persistence, immune dysregulation, and autoimmunity) (Yong, 2021). Risk factors associated with development of long COVID are not yet clear. However, preliminary studies suggest that age, female sex, number or severity of early symptoms, and some pre-existing conditions may be associated

with an increased likelihood of developing this condition (Yong, 2021).

The most common persisting symptoms of long COVID are also frequently reported in patients diagnosed with Lyme disease and other tick-borne illnesses. The clinical burden of long COVID continues to increase as the COVID-19 pandemic continues. Current studies on long COVID are leading to improved understanding and awareness among clinicians regarding the incidence and severity of infection-associated chronic illness. Already, significant financial and scientific resources are being devoted to evaluating the etiologies of long COVID, as well as the management of this disease. Studies to evaluate clinical similarities and common etiologies for long COVID and for other infection-associated chronic illnesses may provide insights into improved clinical management of patients with tick bite–associated chronic illness, including Lyme disease–associated chronic illness. These observations are the basis for recommendation 5.4 in this report.

Health Equity Concerns

An understanding of the clinical presentation and pathogenesis of tick-borne diseases is an essential step to ensuring that patients receive optimum care. Yet a review of the literature shows scant evidence of tick-borne disease research and little written or pictorial representation of the clinical presentation and pathogenesis in Black, Indigenous, and persons of color and other underserved groups. In addition, the absence of reported incidence of tick-borne diseases in these groups adversely impacts the ability to determine accurate information about clinical presentation. The disparate evidence of presentation in underserved groups directly influences the ability of clinicians and researchers to study and learn about pathogenesis in these populations.

According to CDC, structural determinants are defined as "processes and policies that lead to unfair practices, such as inequitable distribution of funding across communities. Social Determinants of Health (SDOH) include health, income, employment, housing, environment quality, education,

transportation, etc." (CDC, 2021a; U.S. Department of Health and Human Services, 2022). These barriers are contributing factors to challenges that patients experience such as delayed or improper diagnosis, exacerbation of symptoms, protracted treatment-chronicity, mental health issues, disability, and even death. Consequently, structural and social determinants of inequity lead to individual- and community-level disparities that further complicate the tick-borne disease patient experience.

The foundational challenge for health equity in persons with tick-borne diseases and associated illnesses is the overall lack of data for all populations defined in the Executive Order on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government (The White House, 2021). Improved data will allow researchers to better understand disease incidence and prevalence in underserved groups. Accordingly, improvements can take place in clinical presentation and pathogenesis. An improved understanding of the clinical presentation and pathogenesis of tick-borne diseases will support patients in underserved groups in receiving improved care. These findings provide the basis for Recommendation 5.2.

Big Picture Summary

Increasing numbers of people are at risk for tick-borne diseases each year in the United States, particularly in areas where these illnesses may not have been previously established. Efforts are badly needed to increase the awareness, both of health care workers and the public, regarding the changing patterns of risk. Health care providers must be able to apply the appropriate diagnostic procedures and therapeutic options and to recognize and treat tick-borne illness in the full range of clinical presentations, thus minimizing the risk of more serious outcomes, including death. Additional research is badly needed to better understand the pathogenesis of tick-borne illness so that safe and effective treatment is available for all.

Chapter 6
Diagnostics
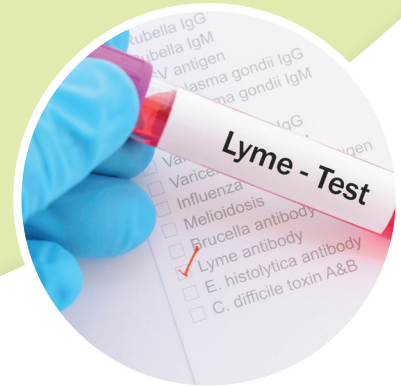
Recommendations Diagnostics

Recommendation 6.1: Convene a panel of stakeholders and experts in tick-borne disease diagnostics, including but not limited to researchers, government, investors, small businesses, large clinical labs, patient advocates, and diagnostics companies, with the goal of promoting the evaluation and development of current and promising new diagnostic approaches.

Rationale

This priority will serve to engage all stakeholders in promoting new technologies and promising candidate diagnostic tests for tick-borne diseases and associated illnesses.

Recommendation 6.2: Recommend increases in federal funding (CDC or NIH) to: (1) build a national biorepository of human clinical specimens for tick-borne disease supported by a national network of qualified labs and physician clinics; and (2) build a clinical and translational research program involving a network of clinical and academic centers.

Rationale

Samples that broadly reflect the patient populations and disease manifestations and are accompanied by thorough clinical case descriptions are needed to adequately assess diagnostic test performance.

Recommendation 6.3: Provide federal support for tick-borne-disease diagnostics through an innovation pipeline with direct Congressional appropriations for a tick-borne-disease innovation accelerator and system that provides targeted funding opportunities, use authorization, lab-to-market commercialization, and implementation via relevant federal agencies.

Rationale

The Working Group's Diagnostics Subcommittee did not find an absence of new technologies or interest in tick-borne disease diagnostics; rather the investment in the future of these tests is a major gap hindering the transition of novel research findings to improved patient outcomes.

Background

Lyme disease and associated tick-borne infections currently constitute a public health crisis. In North America alone, the number of persons who are diagnosed with Lyme disease annually is estimated to be near half a million (CDC, 2021c; Kugeler et al., 2021). Compounding the public health significance is the high rate of other tick-borne infections and co-infections, such as Babesia parasites, multiple species of *Anaplasma*, *Ehrlichia*, and *Rickettsia* bacteria, and several viruses. In addition, the role of *Bartonella sp.* bacteria in complex tick-borne disease warrants further research. Given the limited sensitivity of the most widely used diagnostic test for Lyme disease, the two-tier serologic test, new diagnostic tests are critically needed.

While the two-tier test's lack of sensitivity in early infection is well established, sensitivity in later disease is also less than ideal (Logigian et al., 1999); therefore, the need for testing accuracy at all stages of disease is of the highest priority. Major challenges include the paucity of bacteria in the blood and other body fluids and variable antibody responses to infection, including possible seronegativity due to the capacity of *Borrelia burgdorferi* to suppress immune responses (Dattwyler et al., 1988; Tracy & Baumgarth, 2017).

Many new technologies have been applied to diagnostic testing for Lyme disease, and promising new assays are on the horizon. These tests fall under the categories of direct, indirect, and biomarker detection (Figure 16). The new developments include improvements to serologic tests, sensitive molecular detection, and "omics" approaches such as metabolomics and immune profiles. Opportunities for personalized medicine include host genetic analyses and prognostic indicators of disease or response to treatment.

Because early diagnosis of Lyme disease and other tick-borne diseases clearly results in improved outcomes, the investment in diagnostic testing should include increases in targeted federal funding, improvements in the product development pipeline, and access to adequate patient samples for validation of novel diagnostic tests. The federal government

should pursue multiple avenues—a multi-pronged strategy with coordinated efforts across the U.S. Department of Health and Human Services (HHS), Food and Drug Administration (FDA), National Institutes of Health (NIH), the Centers of Disease Control and Prevention (CDC), and all sectors—to develop novel diagnostic tests and move new diagnostics to market as quickly as possible.

Critical to advancing diagnostic solutions for established and emerging tick-borne diseases is a better understanding of the diagnostic tools currently available and new technologies and approaches currently in development. To generate the content for this chapter, the Working Group's Diagnostics Subcommittee considered the current knowledge of risk factors for pathobiology of tick-borne pathogens, disease pathogenesis, approaches to establishing evidence of infection in patients, and the increased number of tick-borne diseases cases in the United States. The subcommittee assessed the state of diagnostic science and commercial offerings, identified current and future strategies for increasing the sensitivity and specificity of detection, and examined barriers to the development and commercialization of diagnostic technologies and approaches. The subcommittee's work is synthesized in this chapter, which builds on the previous Working Group reports and recommendations.
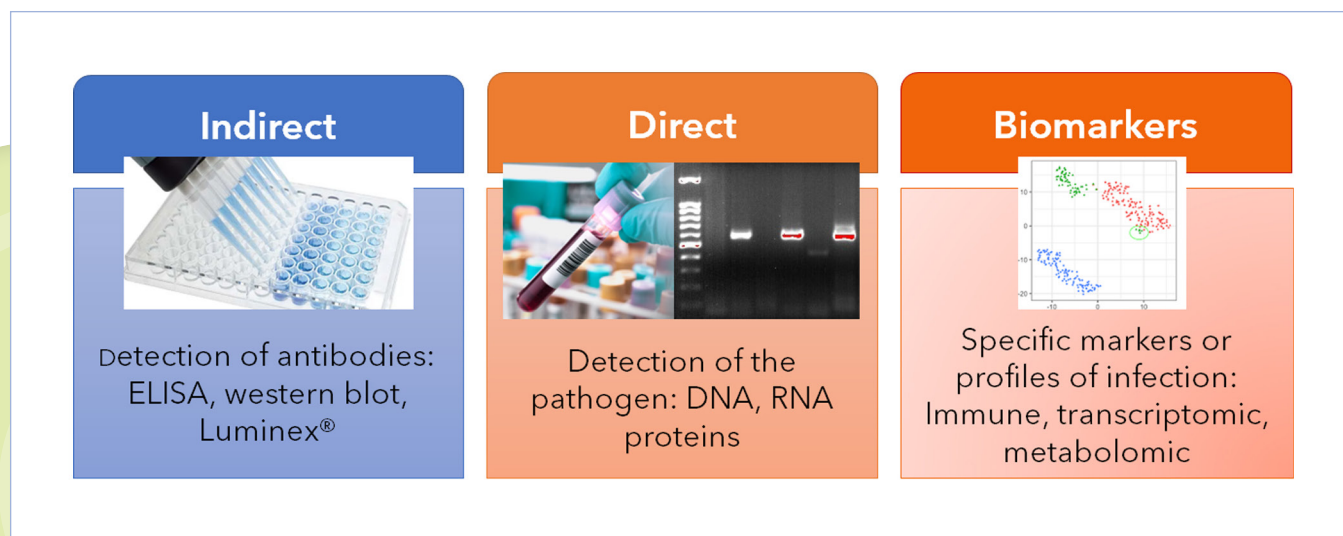

Indirect	Direct	Biomarkers
Detection of antibodies: ELISA, western blot, Luminex®	Detection of the pathogen: DNA, RNA proteins	Specific markers or profiles of infection: Immune, transcriptomic, metabolomic

Figure 16. Diagnostic strategies for tick-borne infections.

The 2018 and 2020 Reports to Congress

Gaps in the ability to diagnose and detect tick-borne diseases were also addressed in both the 2018 and 2020 Tick-Borne Disease Working Group Reports to Congress. The 2018 report recommended increased federal investment to evaluate new technologies or approaches for the diagnosis of Lyme disease and other tick-borne diseases and to include special populations, especially children, in diagnostic studies. The report argued that including diagnostic test development and implementation as part of the federal response would decrease the number of missed diagnoses and reduce the number of people who have short- and long-term negative health effects due to untreated infections. Including pediatric patients and other under-represented patient populations in studies would help ensure that diagnostic tools for Lyme disease and other tick-borne diseases are appropriate for these populations. The 2020 Report to Congress emphasized the need for investment to develop diagnostic tests to detect and differentiate acute rickettsial, ehrlichial, and anaplasmal infections as well as the broader range of tick-borne illnesses, including tick-borne relapsing fever and Powassan virus. In particular, the need for better diagnostic tools, clinical guidance, and surveillance for Alpha-gal Syndrome was emphasized. Investment in all of these diagnostics would enable early diagnosis and intervention.

Diagnostic Testing for Multiple Tick-Borne Diseases and the Potential for Serodiagnostic Test Improvement

Serologic assays (enzyme-linked immunosorbent assays [ELISAs] and western blots) that detect *Borrelia*-specific antibodies have become the standard tests used to diagnose Lyme disease. In typical infections, antibodies (immunoglobulins, or Ig) begin as immature isotype M antibodies (IgM) and then become more specific isotype G (IgG) antibodies. Following infection, IgG antibodies usually develop within 28 days, but some may take as long as 6 weeks. Tests currently accepted for diagnosis of Lyme disease are (a) the standard two-tier test (STTT), consisting of an ELISA with confirmatory western blot, and (b) the modified two-tier test (MTTT), consisting of a multi-antigen ELISA followed by a single antigen (C6) or other multi-antigen ELISA (Branda et al., 2011; Mead et al., 2019). Challenges to the reliability of these tests are the variable antibody responses among infected individuals, unusual persistence of the IgM response, and delay in detectable IgG levels, which reduce sensitivity of serological tests in early-stage Lyme disease.

The blacklegged tick (*Ixodes* spp.), also called the deer tick, is the most medically important arthropod in the United States in terms of the pathogens transmitted. In addition to Lyme disease, at least four other serious illnesses are caused by infectious agents transmitted by this tick vector. These include babesiosis, anaplasmosis, *B. miyamotoi* infection, and Powassan virus infection, any of which may be severe or fatal in compromised hosts. Diagnostic testing for these illnesses is only available from a limited number of clinical laboratories, and methods are not standardized, partly owing to the absence of assays cleared by FDA for any of these infections. The strengths and limitations of available testing specific to each infection are presented in Text Box 1. Other medically important ticks include the American dog tick (*Dermacentor variabilis*), lone star tick (*Amblyomma americanum*), Gulf Coast tick (*A. maculatum*), and numerous others. Diagnosis of the myriad infections vectored by these ticks involves similar challenges as those enumerated in Text Box 1 for the blacklegged tick.

Text Box 1. Diagnosis of Infections Transmitted by Blacklegged Ticks

Babesia spp. (babesiosis)

Agent Description

Blood-borne protozoan parasite. Infects red blood cells.

Recommended Diagnostic Testing

Direct detection in peripheral blood using nucleic acid amplification tests (NAATs) or blood smear examination. Serologic testing is occasionally indicated instead or in addition. The standard method is indirect fluorescent antibody (IFA) testing using whole parasite antigen.

Strengths

Direct detection methods are sensitive and specific.

Limitations

NAATs may not detect all relevant *Babesia* spp., depending on assay design. NAATs may remain positive for months or years after appropriate therapy and symptom resolution. Blood smear examination requires a skilled microscopist and is time consuming and labor intensive. Serologic testing cannot reliably distinguish active from past infection using single-sample analysis, and may not detect antibodies directed against all relevant species.

Needs

- Commercially available NAAT kits cleared by the U.S. Food and Drug Administration.
- Develop single tests capable of detecting all relevant species.
- Develop assays that can confirm disease eradication in compromised hosts after therapy.

Anaplasma phagocytophilum (anaplasmosis)

Agent Description

Intracellular bacterium targeting granulocytes.

Recommended Diagnostic Testing

Direct detection in peripheral blood with NAATs or smear examination, and/or serologic testing using IFA performed on paired (acute- and convalescent-phase) samples.

Strengths

NAATs are sensitive when applied early during the course of infection and before initiation of antimicrobial therapy. Paired serology is a sensitive confirmatory method to establish the diagnosis retrospectively in the convalescent phase of illness.

Limitations

NAAT sensitivity declines after first few weeks of infection and after initiation of antimicrobial therapy. Serologic test sensitivity is poor at the time of initial clinical presentation. A single positive serologic test result does not reliably distinguish active from past infection.

Needs

- Determine optimal molecular and serologic assay designs.
- Determine best diagnostic testing method at timepoints throughout the course of infection.
- Develop direct detection assays with high sensitivity throughout the period of active infection.
- Develop serologic tests that can differentiate active from past infection using single sample analysis.

Borrelia miyamotoi (tick-borne relapsing fever)

Agent Description

Relapsing fever spirochete causing blood-borne infection and meningoencephalitis.

Recommended Diagnostic Testing

Direct detection in blood or cerebrospinal fluid using NAATs and/or serologic testing of paired samples using GlpQ enzyme-linked immunosorbent assay (ELISA) and/or western blot.

Strengths

NAATs are highly specific and have high analytical sensitivity. GlpQ serology does not cross-react in patients with *B. burgdorferi* infection.

Limitations

The possibility of a false negative result in the early days to weeks of infection and inability of a single positive test to distinguish active from past infection necessitate analysis of paired samples when serologic testing is used for clinical diagnosis and the initial test is negative. Existing serologic tests are non-quantitative and do not provide a titer. The clinical performance characteristics of NAATs and serologic tests for B. miyamotoi infection are incompletely understood.

Needs

- Determine optimal molecular and serologic assay designs.
- Determine best diagnostic testing method at timepoints throughout the course of infection.

Powassan virus

Agent Description

Tick-borne flavivirus causing viremia and meningoencephalitis.

Recommended Diagnostic Testing

Direct detection in blood or cerebrospinal fluid using NAATs, and/or serologic testing.

Strengths

NAATs are highly specific and have high analytical sensitivity. The standard serologic method, plaque reduction neutralization testing (PRNT), is highly specific. Clinical sensitivity of either method is incompletely understood.

Limitations

No single method is optimal at all clinical timepoints, necessitating use of both NAATs and serologic tests in most cases. Reactivity in the PRNT assay may lag behind ELISA positivity, yet ELISAs are inadequately specific to stand alone without PRNT confirmation or demonstrated fourfold change in antibody titer using paired samples. PRNT is slow and labor-intensive, requires extensive experience, and is risky for the lab worker.

Needs

- Determine optimal molecular and serologic assay designs.
- Determine best diagnostic testing method at timepoints throughout the course of infection.
- Develop quantitative stand-alone serologic assays on convenient platforms.
- Biomarker discovery (protein antigen detection or indirect markers) to detect cases that may be missed by NAATs and serologic tests.

Sources: Krause et al., 2021; Madison-Angenucci et al., 2020; Wormser et al., 2006.

Opportunities include the use of serologic tests for diagnosis at later stages of disease, improvement of early test sensitivity with combined IgM/IgG testing, and identification of antigen targets that induce the earliest antibody responses. Some evidence also indicates that broader antibody responses are predictive of antibiotic treatment efficacy (Blum et al., 2018). New cytometric bead-based assays utilizing borrelial peptides or whole proteins hold the promise of improving serodiagnostics beyond STTT and MTTT (Radtke et al., 2021). Recent evidence indicates that autoantibodies targeting phospholipid antigens arise in early Lyme disease and may offer more

sensitive detection than STTT (Gwynne et al., 2022). Given the high prevalence of multiple pathogens in ticks, an opportunity exists not only in improving diagnostic tests for all tick-borne diseases, but also in testing ticks for specific pathogens post-exposure.

Vector Testing for Endemicity and Patient Exposure

An underutilized and often overlooked tool in the diagnostic toolbox is testing of the ticks themselves. Unlike mosquitoes, which bite quickly and then disperse, ticks may remain attached for up to 1 week to feed. This provides an opportunity to find and

remove the tick before it has completed a blood meal. Through passive surveillance programs, experts can identify these medically relevant ticks and test them for pathogens to aid clinicians in arriving at a clinical diagnosis should symptoms occur. Tick identification can be complicated, so a layperson or even a clinician can easily misidentify a tick and draw incorrect conclusions about which diseases may be associated with that tick bite (Kopsco et al., 2021). Tick identification can be improved with specific training of health care professionals (Butler et al., 2017). Direct molecular testing, such as polymerase chain reaction (PCR), can be used to detect viral and bacterial pathogens inside the tick. These pathogens can be abundant in the ticks themselves and are generally much easier to detect in the tick than in the host. Different pathogens are also transmitted from the tick to the host at different rates; engorgement status can be used to assess how long the tick has been attached and thus provide clues about the likelihood of pathogen transmission.

Among other groups, local and state health departments, Department of Defense programs, and university-affiliated labs have established successful tick testing services, which provide medically relevant information to tick-bite victims and their health care providers. These passive surveillance programs are also sources of a wealth of information regarding prevalence and distribution of ticks and tick-borne pathogens, especially as they change in response to shifting climate and urbanization. In combination with the published results of active surveillance, these datasets provide critical context to clinical decision-makers so that emerging and endemic diseases are appropriately considered when making a diagnosis. The capacity to conduct these testing programs free of charge is largely limited by inconsistent funding (Mader et al., 2021). For maximum efficacy, these passive surveillance programs should be widespread, subsidized, and held to high-quality testing standards, such as confirming multiple genes for each pathogen or sequence-confirming results. Further, results must be confirmed quickly to aid in prompt diagnosis and should include information about the relative risk of infection attributed to that

specific bite (CDC, 2021f). Marrying conscientious tick testing programs with other diagnostic tools provides an opportunity to identify at-risk individuals before disease sets in and thus should be considered a useful component of personalized medicine for tick-borne diseases and associated illnesses.

"Omics" Approaches

The application of "omics" approaches, which broadly fall under the headings of genomics, transcriptomics, proteomics, and metabolomics, has been promoted as a potential approach to the development of improved diagnostics for infectious diseases, including Lyme disease. The power in these approaches centers on their ability to capture large quantities of molecular or biochemical data in an unbiased and untargeted manner. The primary concept behind the use of omics approaches is that unbiased omics data collection of specific molecular feature types (e.g., proteins, transcripts, or small molecules) can be exploited by machine learning and other computational approaches to define a minimal signature of host molecules that serves as a diagnostic biomarker of specific tick-borne infectious diseases. Further, the defined set of molecules that comprise the diagnostic biomarker can be measured using existing clinical laboratory technologies or emerging technologies that are tractable for clinical applications. In some cases, an omics technology or approach could possibly be utilized for direct detection of the infecting pathogen. Examples of this technology include metagenomic sequencing to detect pathogen genetic material or targeted/semi-targeted proteomics to detect pathogen-specific proteins or peptides.

A wide variety of omics approaches have been investigated for use as potential platforms for tick-borne infectious disease diagnostics or to select panels of features that serve as diagnostic biomarkers. These approaches includes transcriptomics (Bouquet et al., 2016; Petzke et al., 2020), multiple proteomics approaches (Douglas et al., 2011; Magni et al., 2015, 2020), metabolomics (Fitzgerald et al., 2020, 2021; Molins et al., 2015, 2017; Pegalajar-Jurado, 2018), and metagenomic

sequencing (Kehoe et al., 2022; Pritt, 2021). The use of machine learning to discriminate Lyme disease from other diagnoses has been employed with biomarker selection and clinical diagnosis, with the possibility of application to host signature-based diagnoses (Burlina et al., 2019; Joung et al., 2020; Kehoe et al., 2022; Radtke et al., 2021; Tran et al., 2021). Most of these studies have been directed at Lyme disease, and most have served as proof of concept for their use. In at least one case, a specific proteomics approach is being applied as a Clinical Laboratory Improvement Amendments (CLIA)-based diagnostic assay for Lyme disease (Magni et al., 2015).

Sensitive Molecular Testing for Direct Detection

An alternative to serology is testing aimed at direct detection of the pathogen. Direct detection tests have historically been performed using molecular assays such as PCR. These approaches have several advantages over serology: direct detection identifies an active infection; no lag period is necessary for the development of an antibody response; and multiplex assays have the capacity to test for more than one agent. However, molecular testing has not been useful for the diagnosis of Lyme disease, primarily because of transient and limited quantity of bacteria in blood.

Within the past decade, the advent and widespread implementation of next-generation sequencing (NGS) has provided a unique opportunity to overcome the previous limitations of molecular testing. Unbiased NGS detection tests facilitate simultaneous detection of all agents in a clinical sample, while employment of agent-specific oligonucleotide probes for enrichment of desired nucleic acids vastly improves assay sensitivity and provides a detection capability far superior to PCR (Briese et al., 2015). Specifically, a capture sequencing assay for 11 of the most common tick-borne pathogens has been developed (Jain et al., 2021). In addition, technological advancements have resulted in a decrease in costs, labor, and length of time required for NGS data generation and analyses (Gu et al., 2021). The development of portable sequencers has created the potential to establish

NGS as a field-deployable frontline platform, and perhaps even as point-of-care testing in the future (Smith et al., 2020).

The development and recent application of droplet digital PCR (ddPCR) also offers strong potential for overcoming the limitations and low sensitivity of PCR testing, especially in combination with sample enrichment methods (King et al., 2017; Maggi et al., 2020, 2021; Wilson et al., 2015). Although currently quite high, the costs of ddPCR equipment and reagent will decrease over time as clinical applications increase, regulatory standards are established, and insurance reimbursements are determined. Recent advances in ddPCR technology could provide additional affordability in the form of multiplex assays in which multiple infections could be confirmed in a single patient sample (Maggi et al., 2021).

Opportunities for Personalized Medicine

Personalized medicine can be provided in many forms. Tick-borne diseases, with their variance in response to infection and disease presentation between individuals, provide an opportune example of the application of personalized medicine. Here, personalized medicine may take the forms of prognostic indicators of disease resolution and antibiotic efficacy, determination of genetic predisposition for specific manifestations of disease, and immune correlates of acute versus chronic disease.

One example of the use of genomics as a support tool for clinicians comes from work with autism spectrum disorders. Through analyses of single nucleotide polymorphisms (SNPs), deletions, or mutations in a patient's genes, information can be gleaned from the affected metabolic, developmental, or immunologic pathways (Way et al., 2021). The affected genes can then be modulated with natural or synthetic therapeutics to provide balance in the pathways leading to disease or dysfunction. Although much remains to be learned of how genomics can inform treatment for Lyme disease and other tick-borne diseases, the association has been made

Alex Hudson

Alex Hudson experienced years of symptoms before being diagnosed with Lyme disease in 2017. Her mother, Jody, has spoken about the difficulty of finding a proper diagnosis and treatment for Alex: "I couldn't look my child in the eye and explain [that] **doctors simply didn't understand her disease**. There were no more hospitals to be admitted to, no more doctors to reach out to, and no more answers to our questions. There was nothing more that I could do to help my child. As a mother, I was supposed to fix things. But I couldn't fix this."

between variation (a specific combination of SNPs) in the ABCB1 transporter gene and development of post-treatment Lyme disease (PTLD) (Lyon & Seung, 2019). Regarding immune function, SNPs of toll-like receptors and interleukin-6 promoter have also been linked to persistent symptomatology and disease (Hein et al., 2019; Strle et al., 2012).

Another example of research to enable personalized medicine includes the identification of biomarkers for disease states. In one study, chemokines and cytokines in the serum of patients were quantified in a multiplex platform, demonstrating differences that correlated with disease states. Specifically, elevation in the chemokine CCL19 after treatment of early Lyme disease has been associated with the later development of PTLD (Aucott et al., 2016; Soloski et al., 2014). A hindrance to the broad application of these findings to new diagnostic tests is the small sample sizes used to generate the data. Increased funding and human sample availability would help to bolster the translation of such novel findings into commercialized tests.

Current Availability of Patient Samples for Testing and Validation

Well-characterized human biologic samples are vital for conducting research, particularly when developing and validating diagnostic tests for tick-borne diseases and associated illnesses. When performing assays, test developers must know the following information associated with the patient samples collected: signs and symptoms of disease and other relevant health history; what biologic materials were collected; when these materials were collected in the course of disease; how samples were processed and stored; and how samples where characterized, including any PCR, serology, or other laboratory testing that was performed.

In addition to diagnostic test developers and researchers, well-characterized sample repositories also benefit medical providers, patients, and the greater public at risk for Lyme disease (Molins et al., 2014). Currently, three established Lyme disease repositories exist: the CDC Lyme Serum Repository

(Molins et al., 2014), the Lyme Disease Biobank (Horn et al., 2020), and the Study of Lyme disease Immunology and Clinical Events (SLICE) at the Johns Hopkins Lyme Disease Research Center (Rebman et al., 2015). Further, some investigators maintain their own sample collections. Each biorepository has distinct inclusion/exclusion and sample characterization criteria. Although well-characterized Lyme disease patient samples are available, they must be replenished as they are used by investigators working on Lyme disease. For other tick-borne diseases, extremely limited well-characterized samples are available, particularly for the more rare pathogens, such as Powassan, Bourbon, and Heartland viruses.

Challenges to Novel Test Commercialization

Commercialization of diagnostics through the current regulatory review (CLIA for lab-developed tests and FDA for medical devices; Testing.com, 2021a, 2021b2) and test adoption are a part of a complicated process that is fraught with obstacles. This process involves many steps, including clinical research, publication in medical guidelines, physician education, and verification of insurance coverage. Moreover, the process is prohibitively expensive with considerable economic disincentives for investors (Faruki & Lai-Goldman, 2010). Time to sustainable market adoption can take decades, and costs range from $31 million to $94 million per test application (Kirsch, 2019) with no guarantee of a return on investment (Figure 17).
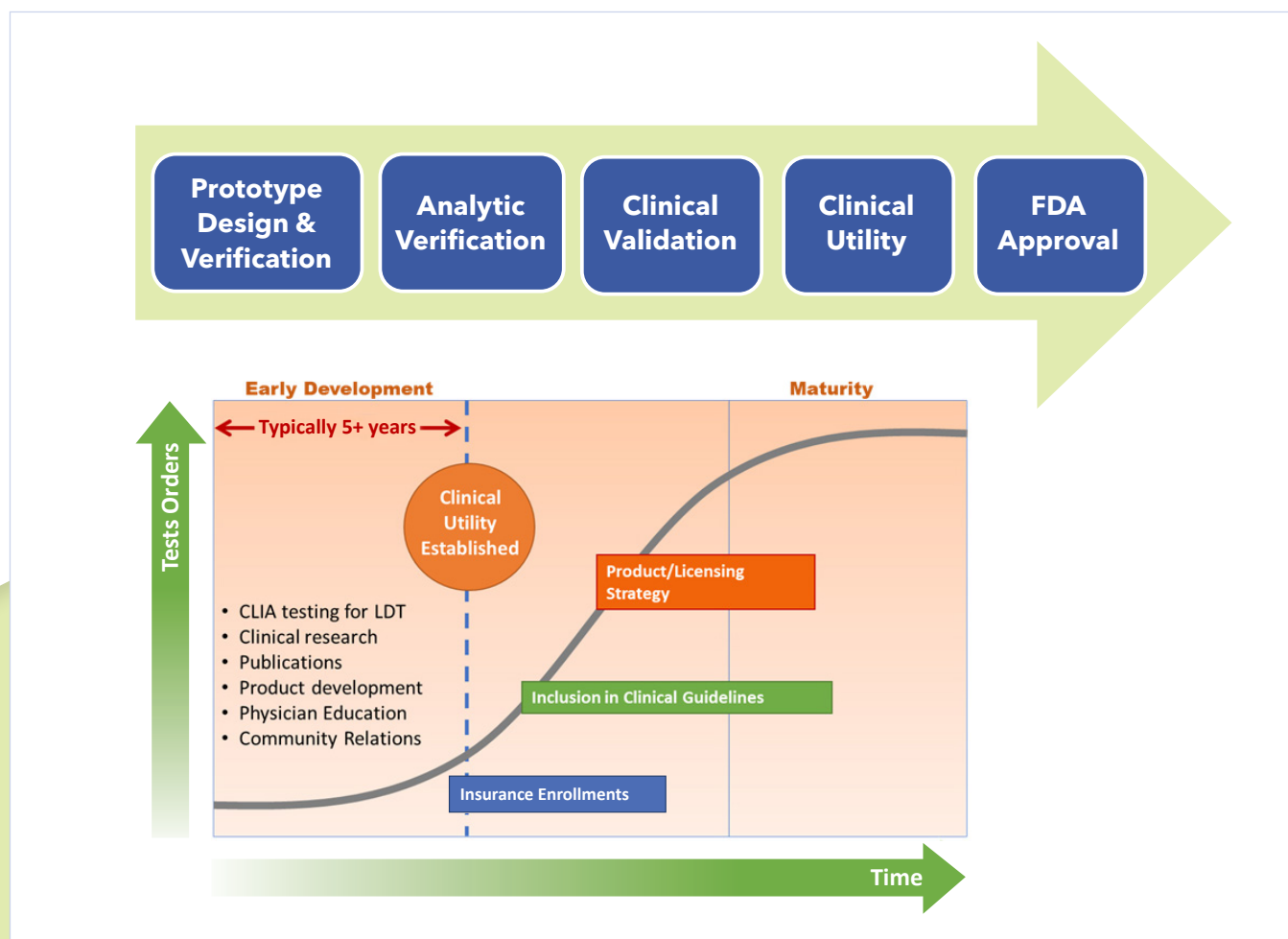
Figure 17. Diagnostic test development pipeline with the commercialization pathway.
Source: Adapted from Lai-Goldman & Faruki, 2008.

Importantly, the United States already faces a shortage of testing innovations, and calls for stricter regulation, such as the Verifying Accurate, Leading-edge IVCT Development (VALID) Act, could further interfere with access to new and better testing (Shirts, 2020). At this time, the FDA approval pathway is especially challenging for new and rare diseases, including many tick-borne diseases, for which the market size may not justify the investment and for which test designs must remain customizable or flexible.

Prior Working Group reports called specifically for development of FDA-approved tests, but not all tests are suitable for scale as a medical device (i.e., in vitro diagnostics or test kits) or testing equipment. Historically, the bulk of clinical testing in the United States has occurred in the category of lab-developed tests (Pew, 2021). FDA sometimes reviews and certifies lab-developed tests, but this activity is not common and can significantly increase commercialization costs. The lab-developed test pathway enables the development and commercialization of laboratory testing as a service in which clinicians interpret the results. However, this regulatory path to market presents its own challenges in terms of variable levels of published scientific evidence for new test methods, the need for clinician and patient education to support proper adoption and clinical use, and the lack of transparency around certain labs offering new tick-borne disease test options.

Regulatory uncertainty, in addition to the political controversy surrounding tick-borne disease testing, creates disincentives for investors, physicians, patients, insurance companies, and diagnostic companies to advance tick-borne disease testing. The unfortunate result is that the most promising diagnostic advances become stuck in the innovation pipeline, failing to move out of the research lab and into clinical practice or stalling at an early stage of clinical proof as a lab-developed test. Navigating such a complex and contentious marketplace is difficult for health care consumers and providers, and commercializing new diagnostic technologies in compliance with best practices in diagnostic innovation is onerous for medical labs. Challenges may be further complicated by insufficient efforts to provide consumers and clinicians with guidance on tick-borne disease test recommendations. Indeed, commercializing new diagnostic technologies under a broadly focused direct-to-consumer business model (Rutschman, 2021) is much easier than commercializing new clinical tests as lab-developed tests available with a doctor's order. However, the latter may fill a critical gap in testing for specific diseases.

The HHS Advanced Research Projects Agency for Health (ARPA-H), established in 2022, can make these pivotal investments in break-through technologies and broadly applicable platforms, capabilities, resources, and solutions that could transform important areas of medicine and health for the benefit of all patients and that cannot readily be accomplished through traditional research or commercial activity. ARPA-H should drive progress by creating a tick-borne disease diagnostics program.

In collaboration with the existing LymeX Innovation Accelerator and the LymeX partnership at HHS headquarters, a new ARPA-H program for tick-borne disease diagnostics could bridge the lab-to-market "valley of death" and move emerging technologies from bench to bedside. ARPA-H for tick-borne disease diagnostics would help to align diagnostics efforts across HHS including FDA, CDC, and NIH to

- speed application and implementation of health breakthroughs to serve all patients;
- foster breakthroughs across various levels—from the molecular to the societal;
- build capabilities and platforms to revolutionize prevention, treatment, and cures in a range of diseases;
- support "user-driven" ideas focused on solving practical problems that advance equity and rapidly transform breakthroughs into tangible solutions for all patients;
- focus on multiple time-limited projects with different approaches to achieve a quantifiable goal;

- use a stage-gate process, with defined metrics, and inject accountability through meeting these metrics;

- overcome market failures through critical solutions or incentives; and

- use the Defense Advanced Research Projects Agency (DARPA) as a model to establish a culture of championing innovative ideas in health and medicine.

Thus, the ARPA-H Program aligns well with efforts needed to combat tick-borne diseases. The research and development and early commercialization teams that are publishing clinical evidence of validation and utility and working steadily on clinical evidence, medical education, and insurance coverage need government support to ensure that patients and their doctors have access to the best tick-borne disease diagnostic tools available.

Informed by the findings of the Working Group's 2022 Diagnostics Subcommittee, this chapter outlines priority issues and recommendations aimed at tackling the many diagnostic challenges associated with tick-borne diseases. The Working Group aims to generate opportunities that will pave the way for innovative solutions, assist clinicians in the treatment of their patients, and translate to significantly improved outcomes for individuals affected by tick-borne diseases and associated illnesses.

> There is not an absence of new technologies or interest; rather the investment in the future of these tests is a major gap hindering the transition of novel research findings into improved patient outcomes.

Major Challenges and Issues

Federal funding for tick-borne disease has not increased in proportion to the increased incidence. Funding allocations often lag behind the current disease burden by as many as 10 years (Ballreich et al., 2021), and the financial burden of Lyme disease in both the United States and Europe is staggering (Adrion et al., 2015; Mac et al., 2019). Importantly, as is the case for several other diseases, federal funding does not correlate with disease burden in the United States; disproportionate allocations of NIH funding have gone to HIV, malaria, ebola virus disease, and zika virus.

Notable challenges include the relative scarcity of well-characterized patient samples for use in test evaluation and validation, the lack of standardization of diagnostic tests (evaluation of different tests in different labs), and the lack of appropriate comparators for tests utilizing different platforms. Test performance is most frequently assessed using acute phase patient samples, limiting diagnostic utility for various stages of infection and different disease presentations. Lack of funding has made it difficult for scientists to focus time and energy on the development of advanced techniques. Few individuals who review proposals have sufficient knowledge of the unique pathobiology of *Borrelia* and other tick-borne pathogens, and the funding pools tend to be small and highly competitive for both federal and foundation-based grant sources. Of the technologies that have reached the prototype stage, only a few have progressed to the first stage of commercialization as a lab-developed assay and only one has progressed to the stage of FDA-approved in vitro diagnostics kit (AACC, 2019). Importantly, incentives for investors to support these testing advances are minimal, and the unique challenges presented by tick-borne infections are not considered. Some commercial labs have chosen to sidestep the rigorous pathway to establish clinically proven diagnostic methods through direct-to-consumer testing. The absence of clear standards for validation of tests can also be a hindrance to the development process. Further, test validation is complicated by the

broad extent of clinical and immunological variability in Lyme disease.

Opportunities

Many of the new testing modalities proposed for Lyme disease and other tick-borne diseases have precedence with use in other infectious diseases. Developers have acquired samples from the Lyme Disease Biobank, among other sources. The tests should be vetted with a large variety of patient samples—from those with early acute infection to those with chronic symptoms. The opportunity to acquire small business grants should be utilized, and this program can be expanded. Finally, bringing together stakeholders would offer the benefit of sharing successes and failures, which may accelerate development. The funding and creation of Centers of Excellence focused on tick-borne disease patient outcomes and clinical research could be a critical component of overcoming hurdles for improved diagnostics.

Educating medical experts, disease advocates, and consumers on the development and commercialization pathway for diagnostics could help clarify which technologies hold the most potential for supporting a more accurate diagnosis of disease. For example, CDC could replace its current "Lab Tests Not Recommended" webpage with one that provides guidance to clinicians and consumers on the types of technologies that are in the innovation pipeline with different stages of maturity and various levels of evidence.

Although controversies regarding Lyme disease in the past may have served to hinder the development and advancement of new diagnostic tests, the Tick-Borne Disease Working Group is unified in its recognition of the importance of new and improved testing for the benefit of public health. Educating the American public on the importance of garnering clinical evidence and participating in clinical studies would help establish data and biobanks for research on novel diagnostic approaches, which will speed our movement toward new and actionable clinical understandings of these important emerging diseases.

Creating a national initiative to stimulate interest and funding for tick-borne disease diagnostic test development is imperative to ensuring that these diseases are addressed independently from infections that kill quickly, such as hospital-acquired infections, or those that affect vast populations, such as influenza and novel coronaviruses. Several initiatives designed to draw interest and investment in advancing diagnostic solutions for tick-borne disease are under way, such as the LymeX Innovation Accelerator public-private partnership and the CDC-led national strategy for vector-borne disease. Funds could be allocated to build on the foundation of these programs to expand awareness and investments more rapidly in advancing diagnostics to support both research and clinical use.

Big Picture Summary

The Working Group findings indicate that there does not appear to be a paucity of novel ideas or technologies that are intended to improve diagnostic testing for Lyme disease and other tick-borne diseases. Rather, the path to product development and commercialization is stifled by a lack of funding and support. Using the analogy of NIH small business grant funding mechanisms, many of these candidate diagnostic tests are stuck in the Phase I (optimization, development, and testing) stage. Thus, more investment must be made in the Phase II (path to commercialization) stage. Widespread agreement exists that the most commonly used test (two-tier serology) is not good enough. Many advanced diagnostic testing platforms are already showing improvement over two-tier testing. Although there may never be a single one-size-fits-all test developed to diagnose Lyme disease and other tick-borne diseases, we can certainly do better than what is currently approved, which may require us to consider multiple tiers if necessary.

Chapter 7
Disease Prevention and Treatment

Recommendations

Recommendation 7.1: Improve the quality, timeliness, and completeness of surveillance and reporting of tick-borne diseases nationwide. The resulting information should be used to educate health care providers and the public to prevent, diagnose, and treat tick-borne diseases.

Rationale

Timely and appropriate diagnostic, prevention, and treatment for all tick-borne diseases and associated illnesses require an understanding of the geographic regions where those diseases occur. Up-to-date information must be efficiently communicated to health care professionals to maintain a level of clinical awareness of tick-borne diseases in their area.

Recommendation 7.2: Increase funding to develop multi-pathogen vaccines, "anti-tick" vaccines, and new prevention strategies to provide broad protection against different tick-borne pathogens. Research on stand-alone Lyme disease vaccines should look for alternatives to human OspA-based vaccine approaches.

Rationale

Vaccines are powerful tools for preventing infectious diseases. Market realities for most tick-borne diseases, however, are likely to make single-pathogen vaccines untenable for pharmaceutical development. Multi-pathogen or anti-tick approaches could overcome these barriers. While a Lyme disease–specific vaccine proved effective in the past, and new ones are in development, historical concerns about the outer surface protein A (OspA) antigen persist in the public. Alternative antigens should increase public acceptance of new Lyme disease vaccines.

Recommendation 7.3: Accelerate discovery, preclinical and clinical development of effective treatments for tick-borne diseases. Increase funding for research into understudied areas of treatment for tick-borne diseases, including but not limited to pediatric neuropsychiatric illnesses, pregnancy outcomes in infected women, and persistent post-treatment symptoms in all age groups, with emphasis on Lyme disease.

Rationale

Some individuals treated for Lyme disease continue to report a variety of symptoms or manifest clinical signs of disease. Improved treatments are needed, which requires an understanding of the underlying causes of this ongoing disability. Additional research is therefore needed into the pathogenesis of persistent signs and symptoms, as well as into improved treatments for the full range of sequelae associated with Lyme disease.

Background

Tick-borne diseases are an important and increasing cause of illness and, in some cases, mortality. In the United States, they are the leading cause of vector-borne disease, and changes in tick home ranges are expanding areas of endemicity (Madison-Antenucci et al., 2020). Despite their role in infectious diseases

in both the United States and globally, many tick-borne pathogens—which include bacteria, viruses, and parasites—have not received the attention paid to other infectious diseases. Similarly, the non-infectious allergic disease Alpha-gal Syndrome is less understood than other allergic conditions. Effective prevention and treatment measures are lacking, as is our understanding of the fundamental pathogen and host biology behind the optimal interventions.

The 2022 Tick-Borne Disease Working Group addressed these concerns, first through a subcommittee convened to look specifically at prevention and treatment issues across the tick-borne disease spectrum, and later by the Working Group itself. Previous Working Group reports were also reviewed to determine what issues may have been missed or require additional emphasis. Readers are encouraged to review the subcommittee reports, which have been abridged and summarized in this chapter along with other content generated by the Working Group. Lyme disease, as the most common tick-borne illness in the United States, was discussed last by the subcommittee to allow sufficient time to address the spectrum of issues associated with the disease. That order is retained in this summary, with Lyme disease appearing at the end of this chapter.

Rickettsial Diseases

Bacteria in the order rickettsiales, namely *Ehrlichia*, *Anaplasma*, and *Rickettsia* species, are the second leading cause of tick-borne infections in the United States (Rosenberg et al., 2018). These infections, hereby referred to as rickettsial diseases, can cause serious illness or death, especially if not promptly treated. Although the true incidence and prevalence of these infections are unknown, the diseases caused by this collection of bacteria result in higher rates of hospitalization and death than Lyme disease yet remain clinically underappreciated.

Rickettsial pathogens are transmitted by different tick species, and therefore have distinct, though often overlapping, geographic distributions. They also share some clinical signs and symptoms, while differing in others. This combination of similarities

and differences can complicate recognition and diagnosis, compromising timely treatment and efforts to focus prevention outreach on appropriate regions and risk groups.

Rickettsial pathogens were discussed extensively by the 2020 Working Group, as outlined in the final Report to Congress and in the report by the Rickettsiosis Subcommittee. Rickettsial pathogens were also discussed by the 2018 Working Group, though solely within the context of Lyme disease coinfections. While the two previous reports together provided excellent overviews of rickettsial disease treatment and prevention, the 2022 Disease Prevention and Treatment Subcommittee Report outlines several issues that justify further discussion.

In addition to the rickettsiales, facultative intracellular bacteria of the genus *Bartonella* have been suggested to cause tick-borne illness or Lyme disease co-infections (Berghoff, 2012; Eskow et al., 2001; Maggi et al., 2012; Podsiadly et al., 2003). Despite these reports, evidence is lacking to support tick transmission of *Bartonella* species, including *B. henselae*, the predominant bacteria discussed in this framework (Telford & Wormser, 2010). The pathogen is still often cited as a co-infection with Lyme disease, however, and warrants further research.

Prevention

Approaches targeting the tick or reservoir likely have the best chance of commercial success. Anti-tick vaccine development is an intriguing approach that could prevent multiple tick-borne infections with a single vaccine. Pathogen-specific vaccines, although potentially effective, are unlikely to be commercialized for any of the rickettsial diseases. It is possible, however, that multi-pathogen vaccines—for example those targeting pathogens transmitted by either a single or multiple tick species—would have market viability and should be considered. In that light, research should continue with single pathogen approaches, which could be later combined into multivalent vaccines.

Potential roadblocks to multi-pathogen vaccines may include review requirements that single-pathogen

Gabriella "Gabby" Galbo

Gabriella "Gabby" Galbo was a vibrant 5-year-old, described by her parents as a beautiful soul with a contagious smile that could light up a room. She loved cupcakes, animals, and spending time with her family. Gabby was the youngest of Tony and Liz Galbo's three daughters, and she had a bright and promising future ahead of her. Gabby's life ended too soon, when an untreated tick-borne disease called Rocky Mountain spotted fever (RMSF) led to sepsis and septic shock, to which she ultimately succumbed on May 11, 2012.

Despite multiple visits to her pediatrician and two different emergency rooms, Gabby was continually misdiagnosed. From the time her symptoms appeared to when she was finally diagnosed as septic, Gabby had been misdiagnosed four times, and wrongly sent home with abnormal/critical bloodwork, all of which costed critical time in which she could have been treated and saved. Gabby's autopsy confirmed RMSF, the diagnosis that at least three of her attending physicians had considered but failed to treat despite Gabby's fever, her compatible bloodwork, and the iconic spotted rash spread across her body. Together Gabby's parents, Tony and Liz Galbo, have championed "Gabby's Law," which requires Illinois hospitals to adopt, implement, and periodically update evidence-based protocols that will better recognize and treat sepsis. The legislation received unanimous support in both the Senate and the House and was passed in 2016.

vaccine viability be demonstrated before they can be combined into a multi-pathogen formulation. Perhaps a larger hurdle is difficulty in conducting a vaccine trial for a rickettsial disease, because the relatively low incidence would likely mandate a prohibitively large enrollment.

Canine vaccines against *Rickettsia rickettsii* offer an alternative approach to mitigating large outbreaks or epidemic levels of Rocky Mountain spotted fever (RMSF) that have been identified in the southwestern United States and northern Mexico during the past two decades. In these settings, cases of human disease result from zoonotic infections in dogs and large populations of brown dog ticks (*Rhipicephalus sanguineus*) (Demma et al., 2005). Vaccinating domestic dogs against the pathogen could interrupt the transmission cycle and protect humans from infection in this unique but highly relevant circumstance.

Treatment

Treatments for rickettsial diseases are effective and available, and new therapeutics for acute infections are not a pressing need. Novel therapeutic approaches for late-stage disease resulting from delayed diagnosis, however, should still be pursued. Doxycycline is effective against *Anaplasma*, *Ehrlichia*, and *Rickettsia*, and antibacterial resistance has not been reported (Dumler et al., 2007). There are, however, areas of treatment that could still be addressed. Foremost among these is that although

doxycycline is highly effective, there is a lingering hesitancy among clinicians to prescribe the drug because of outdated concerns regarding its use in children; in actuality, the data indicate that short courses of doxycycline do not cause perceptible staining of permanent teeth (Pöyhönen et al., 2017). Enhanced educational efforts, targeted particularly to all types of frontline health care practitioners, is a critical need.

The pursuit of new prevention and treatment methods should be accompanied by a commitment to surveillance and reporting of tick-borne diseases and associated illnesses. Given the rapid clinical progression of many tick-borne diseases, particularly RMSF, physicians must be sufficiently informed to suspect rickettsial infections in endemic areas in order to quickly initiate appropriate therapy to prevent onset of life-threatening manifestations.

Although new, non-antibiotic adjunctive therapies may be worth pursuing, especially in cases where antibiotic treatment has been delayed, a greater focus should directed toward identifying and treating presumptive cases. That focus requires improved awareness of relevant tick-borne diseases in different geographic areas.

Babesiosis

Babesiosis is a worldwide disease caused by protozoan parasites of the genus *Babesia* (Vannier & Krause, 2009). There are more than 100 species of *Babesia*, 6 of which infect humans, while the others infect a wide array of wild and domestic animals. *Babesia* parasites invade and replicate within red blood cells, and the main route of transmission is through the bite of an infected hard-bodied (Ixodid) tick. *Babesia* can also be transmitted via blood transfusion, organ transplantation, and perinatally from an infected mother to her fetus, but these routes of transmission, although relatively rare, are underappreciated by clinicians.

Babesiosis is an emerging tick-borne disease, with an increasing number of cases reported both in the United States and globally (Kumar et al., 2021). The geographic range of *Babesia* is expanding in the

United States from epicenters in the Northeast and northern Midwest, where *Babesia microti* is endemic. Sporadic babesiosis cases due to *Babesia duncani* have also been reported on the West Coast (Conrad et al., 2006; Kumar et al., 2021), and cases of *Babesia divergens*–like babesiosis have been described in the Midwest and Far West (Herc et al., 2018; Herwaldt et al., 2004; Kumar et al., 2021. Multiple Babesia species that cause disease exist in other countries, and rigorous epidemiological studies suggest that many more cases occur than are reported (Krause, 2019; Vannier et al, 2015).

Prevention

No vaccine or other prophylactic agent is currently available to prevent *Babesia* infection in humans. Further research is needed to study immunogenic *Babesia* proteins, which could become the basis for a monoclonal antibody (mAb) therapy or vaccine. The small market limitations described for the rickettsial pathogens are likely relevant to babesiosis as well.

Treatment

The current standard treatment of babesiosis is the combination of atovaquone/azithromycin, or clindamycin/quinine as an alternative (Krause et al., 2021; Vannier & Krause, 2012). Treatment is less effective for immunocompromised patients. Mild to moderate cases of babesiosis can be successfully treated with a 7- to 10-day course of these regimens (Krause et al., 2000), and hospitalized patients are similarly treated, except that the atovaquone or clindamycin is administered intravenously. Symptoms typically abate within a few days. Highly immunocompromised patients may require months of antibiotic therapy, however, and some die despite treatment (Krause, 2019). Antibiotic resistance can develop during prolonged therapy, highlighting the strong need to develop new therapies for the immunocompromised patient population.

As reported for the rickettsial pathogens, improved surveillance and reporting is needed for the effective treatment and prevention of babesiosis. People living and working in endemic areas, including clinicians, are often unfamiliar with babesiosis. The disease has

a long incubation period (1-4 weeks), and symptoms are nonspecific. There is no easily recognized symptom such as the erythema migrans rash of Lyme disease that establishes the diagnosis.

In addition, because babesiosis is far less commonly reported than Lyme disease and is an emerging infection, many physicians lack an understanding of the dangers it can pose, especially for populations with risk factors for severe disease.

Relapsing Fever/*Borrelia miyamotoi* Infection

Relapsing fever is an arthropod-borne infection caused by several species of spirochetes in the genus *Borrelia* found throughout the world (Krause et al., 2015). Two major types of relapsing fever are classified according to their arthropod vector, tick-borne relapsing fever (TBRF) and louse-borne relapsing fever. Until recently, TBRF has been associated solely with soft ticks of the family *Argasidae*, but that has changed with the discoveries of human infections caused by *Borrelia miyamotoi* (Platonov et al., 2011), which is carried by hard-bodied ticks (*Ixodidae*) (Fukunaga et al., 1995). Although *B. miyamotoi* is phylogenetically grouped with the relapsing fever bacteria, it shares some phenotypic characteristics of the Lyme disease spirochetes.

Soft-bodied TBRF has been reported in 14 Western states (CDC, 2015). *B. miyamoti* is geographically associated with the range of its primary hard-bodied tick vectors, *Ixodes scapularis* and *I. pacificus*, which are also the vectors for Lyme disease in the United States. Although the general geographic ranges of relapsing fever spirochetes are known, their incidence and prevalence remain unclear.

Prevention

No vaccine exists to protect against infection with *B. miyamotoi* or the soft-bodied tick-transmitted relapsing fevers. The market considerations indicated for the rickettsial diseases likely apply to the relapsing fevers as well, and vaccine uptake would be more likely if protection against babesiosis were included as part of a broader multi-pathogen vaccine.

Treatment

Optimal treatment of *B. miyamotoi* is uncertain. The antibiotics used for Lyme disease—doxycycline, amoxicillin, or ceftriaxone for 10-21 days—are also effective against *B. miyamotoi* infection; however, limited therapeutic studies have been conducted. Furthermore, clinical complications are not thoroughly understood, nor are the risk factors associated with those complications. In addition, diagnosis of *B. miyamotoi* is often not considered, leading to delayed or missed diagnosis. Even when considered, there is a lack of commercially available *B. miyamotoi* tests, and cross-reactivity may occur in enzyme immunoassay tests for *B. burgdorferi*. Improved surveillance and education are therefore important needs.

Tick-Borne Viruses

Emerging tick-borne viruses in the United States include Powassan, Heartland, and Bourbon viruses. The central issue regarding these infections is that little is known about them because of the relative rarity of documented infections, as well as regulatory and funding challenges associated with researching them in an academic setting.

Powassan virus (POWV) is a tick-borne flavivirus first reported in 1958. It is the sole new-world representative of the tick-borne encephalitis serological complex within the flaviviruses. Infection in humans is notable for the severity of acute disease (~10% case fatality rate among reported cases [CDC, 2022c]) and the high prevalence of severe long-term sequelae (Ebel, 2010). POWV is frequently isolated and/or detected in deer ticks (*I. scapularis*), which feed frequently on people and have driven the emergence of Lyme disease and other tick-borne diseases in recent decades. Steady increases in annual caseloads of POWV and documented infection in deer indicate steady emergence due to association with these vectors (Nofchissey et al., 2013). Moreover, because of its association with deer ticks, POWV should be considered the most significant of the known tick-borne viruses in North America.

About 50 cases of heartland virus (HRTV) have been reported in humans in the past decade (CDC, 2022d). HRTV is maintained in nature in transmission cycles that are poorly understood but appear to involve lone star ticks (*Amblyomma americanum*) as vectors to humans. The expansion of lone star ticks to the west and north may bring this virus into new localities, such that additional groups of people will be exposed in the future. Hence, HRTV is an extremely important subject for ongoing research.

Bourbon virus has produced 5-10 known human cases (Kosoy et al., 2015; Savage et al., 2018). The infection may be clinically severe, particularly in older individuals with comorbidities. *A. americanum* ticks are vectors.

Prevention

No vaccines are licensed for use against any of the North American tick-borne viruses. However, vaccines are available for other tick-borne viruses related to POWV, including one (Ticovac®) that was recently licensed for use in the United States in people traveling to countries endemic for tick-borne encephalitis (i.e., Europe and parts of Asia, including Russia, Mongolia, and China). Development of stand-alone vaccines against domestic tick-borne viruses is likely not feasible, but efforts to develop vaccines against general virus classes may offer a solution.

Treatment

No antiviral drugs are currently approved for use against North American tick-borne viruses, although efforts should be made to test antiviral drugs developed for related viruses against POWV, HRTV, and Bourbon virus. MAb therapies have been proposed and tested in mice, and research in that area should continue to be supported.

Alpha-gal Syndrome

Alpha-gal Syndrome (AGS) is an allergy to the carbohydrate galactose-alpha-1,3-galactose ("alpha-gal") that is present in lower mammals such as cows, sheep, pigs, cats, and dogs (Levin et al., 2019). People who develop AGS most commonly report allergic reactions after eating beef, pork, or lamb (Commins

et al., 2014). Unlike more traditional food allergies, reactions to alpha-gal occur 3-6 hours (or more) after consuming mammalian meat, and this prolonged delay frequently creates a challenge in diagnosis (Commins et al., 2014; Flaherty et al., 2017; Levin et al., 2019).

Although it is not fully established how AGS develops, accumulating evidence suggests that tick bites play a causal role (Commins et al., 2011). In the United States, the primary tick associated with AGS is *A. americanum* (the lone star tick) (Commins et al., 2011). However, in other areas of the world different species of ticks have been associated with the allergy (Chinuki et al., 2016; Levin et al., 2019; Van Nunen et al., 2009).

Accumulating data suggest that the incidence of AGS is on the rise, with the highest number of incidences reported in the southeast region of the United States, which correlates with the expanding geographic distribution of lone star ticks (Commins, 2016; Commins et al., 2011; Levin et al., 2019; Pattanaik et al., 2018).

Prevention

As with the tick-borne infections, targeting human-biting ticks may have the best chance of success against AGS. Anti-tick vaccines create "tick resistance" in humans by vaccinating with tick salivary or other factors to induce an anti-tick immune response. This approach could prevent multiple tick-borne conditions with a single vaccine.

Recently, a line of genetically edited pigs was developed that do not express alpha-gal. These "alpha-gal safe" animals have been approved by the U.S. Food and Drug Administration (FDA) and could represent a safe source of porcine medical products (e.g., heart valves) and even pork meat for patients with AGS. Additional studies and testing are recommended to pursue this avenue of prevention.

Treatment

Because AGS is not known to be infectious, the primary treatment involves treating allergic reactions through guideline-based medical management. No controlled studies have been reported for allergen desensitization related to AGS.

MAb approaches are a possible treatment approach. Omalizumab is commercially available for management of allergic asthma and treatment of chronic hives, and may have broader implications in treating conditions mediated by immunoglobulin E (IgE) such as AGS and other food allergies. Trials are under way with omalizumab in peanut allergy, and similar trials should address AGS. In addition, case studies involving thousands of patients who have received a medically-based Soliman Auricular Acupuncture Treatment (SAAT) show up to 96% effectiveness in achieving remission (Bernal et al., 2021; Liebell, 2020; Soliman, 2014); however, randomized controlled trials research is needed to further validate these results. As with the other tick-borne diseases, improved surveillance and reporting are critical to adequate recognition and management of illness.

Lyme Disease

Lyme disease, the most common vector-borne disease in the United States, was covered extensively in the 2018 and 2020 Tick-Borne Disease Working Group Reports to Congress, as well as elsewhere in this current report. Background information on Lyme disease and the causative pathogen, *B. burgdorferi*, is therefore not necessary within this chapter, which will instead focus exclusively on the key issues related to Lyme disease prevention and treatment.

Prevention

Current approaches to the prevention of Lyme disease rely largely on strategies that increase awareness of the threat of tick bites in tick-infested areas, promote the prudent use of proper clothing and/or repellent, and introduce measures that focus on controlling the major animal reservoirs of *B. burgdorferi*. Although these approaches are and will continue to be cornerstones to the prevention of human Lyme disease, several other prevention modalities show promise as prophylactic approaches in the prevention of Lyme disease in the human host. These modalities include new and emerging vaccines, the development of borreliacidal human mAbs, and the use of small molecules.

In 1998, a Lyme disease vaccine (Lymerix) targeting *B. burgdorferi* OspA was licensed and made available, but it was removed from the market in 2002 because of a range of complex factors, and a new vaccine is under Phase 3 clinical trials. The new vaccine contains recombinant OspA proteins from several *Borrelia* strains found in the United States and Europe and has been engineered to remove the amino acids thought by some to drive a potential autoimmune response in some individuals. Preclinical studies and current trials have shown great promise (Comstedt et al., 2017). In addition to this vaccine, an effective canine vaccine using chimeric antigens (a mixture of antigens linked end-to-end) has been developed and brought to the veterinary market, a strategy that has been proposed as an effective human vaccine approach (Camire et al., 2021; O'Bier et al., 2021).

Despite these promising developments, research on new and effective vaccines against human Lyme disease should be expanded. This effort will include the use of next generation vaccine platforms such as messenger RNA (mRNA)-based and viral vector vaccines. In addition, the success of future effective vaccine strategies is strictly dependent on a deep understanding of the elements of the human immune response that are most effective in providing protection against *Borrelia*.

As indicated for the other tick-borne pathogens, anti-tick strategies should be pursued to provide possible broad protection against multiple diseases. During pathogen transmission through a tick bite, the tick also transmits saliva containing several salivary gland proteins that have a range of biological properties (Hovius et al., 2007). Anti-tick immunity induced by vaccination with tick proteins in animal models has been shown to alter and even arrest tick feeding (Matias et al., 2021; Rego et al., 2019). More recently, an mRNA-based nanoparticle vaccine against *I. scapularis* has shown efficacy with a guinea pig model of tick feeding and *B. burgdorferi* transmission (Sajid et al., 2021). Further development of this approach deserves strong support, which should include defining immune targets using relevant animal models and employing well-defined human

cohorts, understanding the human immune response to tick proteins, and developing a safe and specific vaccine approach that will merit clinical trials.

Several pathogen-specific human mAbs have been developed for use as therapeutics. A human mAb (2217LS) reactive to OspA has been developed and engineered to retain an extended blood half-life (Schiller et al., 2021; Wang et al., 2016). This reagent has proven effective in rodent and primate models, has been proposed to be used as a pre-treatment for at-risk individuals, and is now undergoing Phase I trials. This approach, which can impact both prevention and treatment of other tick-borne pathogens, deserves support.

Given past concerns associated with the Lyme disease vaccine and current vaccine hesitancy in the United States, work should be done to prepare for the roll-out of any new vaccine. Such work includes establishing the physical and economic burden of disease and transparent communication with the public and health care providers.

Treatment

Clinicians, scientists, and patient advocates continue to disagree about the optimal treatment courses for Lyme disease. The 2022 Prevention and Treatment Subcommittee recognized the need to gather perspectives from the diversity of viewpoints, and to present those positions to the Working Group. The details of the subcommittee deliberations, including the contrasting viewpoints on Lyme disease treatment, can be found in the subcommittee's report. A general summary follows here.

Lyme disease is a multisystem inflammatory disorder caused by the spirochetes in the *B. burgdorferi sensu* lato complex, and is treated with antimicrobials to resolve the acute infection, avoid complications, and prevent a relapse of the initial infection. As demonstrated in prospectively conducted trials, treatment with appropriate antibiotics early in *B. burgdorferi* infection is effective at preventing the development of later clinical manifestations in the vast majority of patients (Nowakowski et al., 2003). Nevertheless, following the acute phase of infection,

29 percent of patients treated with recommended courses of antibiotics reported moderate to severe symptoms at one year, with an additional 14 percent reporting functional impairments (Aucott et al., 2022). It has been difficult to ascertain the proportion of these patients accurately, and the duration of treatment could influence the outcomes (Aucott et al., 2022; Massarotti et al., 1992); however, systematic methodology has been employed to develop operational definitions. These include development of a standardized test battery to characterize a diverse group of Lyme disease patients, and systematically interviews of a wide spectrum of persons diagnosed with Lyme disease to classify them into symptom archetypes (HHS, 2021; Turk et al., 2019).

Chronic infection has been hypothesized to be the cause of persistent symptoms, and animal studies have demonstrated that biological cure may not be uniformly achieved with monotherapy, such as doxycycline and ceftriaxone (Barthold et al., 2010; Crossland et al., 2018; Embers et al., 2012, 2017; Hodzic et al., 2014), but few clinical trials utilizing combinations of antibiotics have been conducted. Multiple clinical trials of extended antibiotic courses using monotherapy—with the exception of two that found a sustained benefit on fatigue (Fallon et al., 2008; Krupp et al., 2003)—have demonstrated no sustained benefit to the majority of subjects enrolled (Berende et al., 2014; Fallon et al., 2008; Klempner et al., 2001; Krupp et al., 2003). The potential benefit of extended antibiotic courses must be weighed against the risk of side effects, including adverse events of the drug and increasing antimicrobial resistance. Although complete understanding of the molecular mechanisms underlying this condition has not been achieved, autoantigens and/or central nervous system sensitization have been postulated to play a role (Maccallini et al., 2018). Overall, there is a need for enhanced understanding of the pathogenesis of Lyme disease–associated chronic illness to help design interventions to alleviate the suffering of these patients. Addressing this need should include research based on combination antimicrobial therapy and complementary non-antimicrobial interventions.
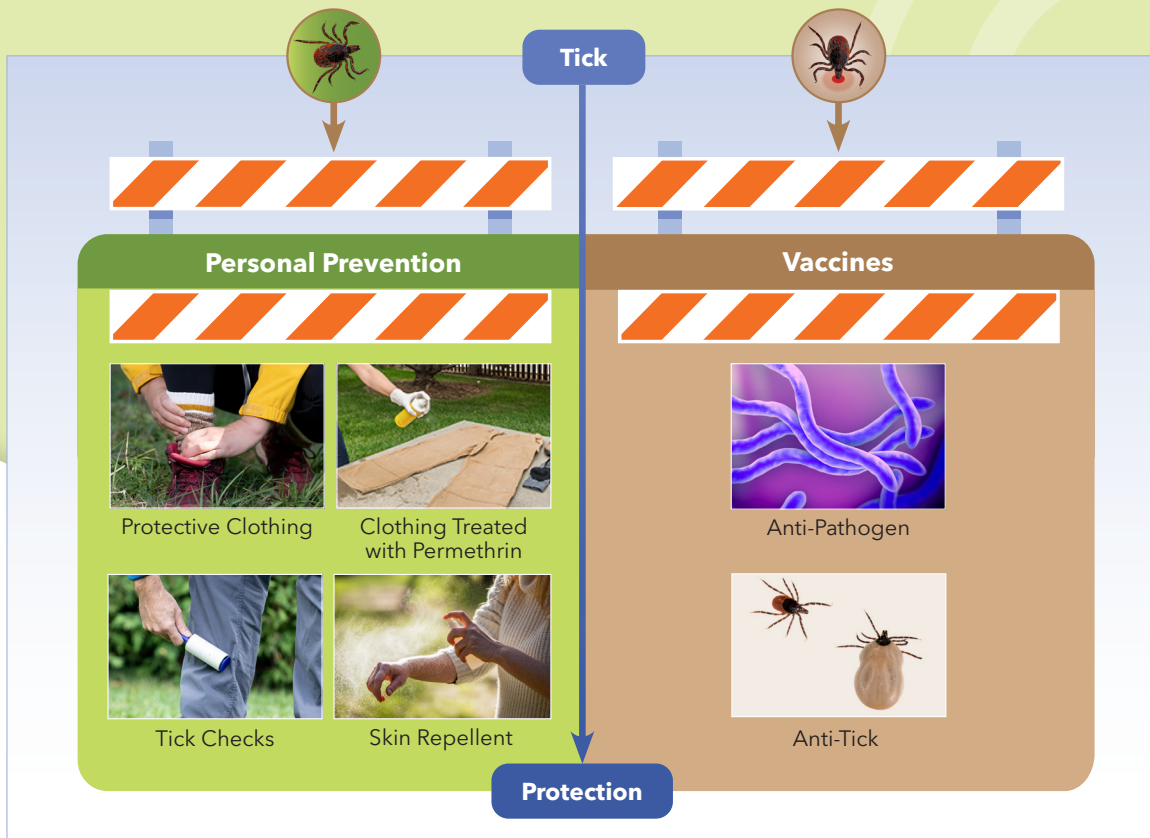
Figure 18. Tick-borne disease prevention through intervention.

Refer to Chapter 3: Changing Dynamics of Tick Ecology, Personal Protection, and Control for additional information on tick bite prevention and control.

Photo credit: CDC.

In addition, the role of initial coinfections needs to be studied in prospective well-designed cohort studies.

Two specific treatment-related issues were addressed by the 2018 and 2020 Working Groups, but warrant additional emphasis because of continuing evidence gaps. These are neuropsychiatric syndromes and Lyme disease in pregnancy. Research is needed to better understand the possible role of Lyme disease and *Bartonella* infections in the pathogenesis of certain pediatric neuropsychiatric syndromes, notably Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), as well as their optimal treatment, including investigation of integrative treatment approaches such non-pharmaceutical interventions that enhance the patient's quality of life. There is a very limited evidence base to guide maternal antibiotic treatment for gestational Lyme disease and for evaluation and follow-up for the potentially infected infant. U.S. consensus recommendations exist to guide

management of pregnant women and infants at risk for syphilis, HIV, Zika virus, and several other congenital infections, but no such guidance for Lyme disease exists.

Big Picture Summary

The Prevention and Treatment Subcommittee, as well as the Working Group as a whole, acknowledged the abundance of gaps and needs across the spectrum of tick-borne diseases. Singling out a few challenges to be addressed by federal agencies is difficult, and a complete list of important needs is not possible. However, the following are overarching needs that should be prioritized.

Awareness and Education

Regardless of the pathogen or disease in question, the need for improved awareness and education rose

to the top of most discussions. Prevention efforts cannot be efficiently targeted, and proper treatment will not be initiated, without an understanding of the incidence, prevalence, and geographic distribution of individual tick-borne diseases. A well-funded surveillance and reporting system, capable of updating our knowledge as tick-borne pathogens expand their geographic ranges, is critical. That information must also be coupled with an education system to bring health care providers up to date on the current state of tick-borne diseases and associated illnesses in their region.

Tick-Borne Disease Prevention

The clinical utility of vaccines has been proven against many infectious diseases, and that promise likely holds for the tick-borne pathogens. Few tick-borne disease vaccines have been advanced beyond early animal studies, representing a gap in the field. Research on vaccines and other immunoprotective strategies should therefore be sustained, beginning with understanding the correlates of immune protection and applying those discoveries to the development and testing of new vaccines in people. As previously indicated, however, market considerations will likely hinder the advanced development of single-pathogen vaccines, especially for low-incidence infections. Federal agencies should therefore encourage and support research on multi-pathogen approaches and anti-tick vaccines. Vaccines targeting the tick bite itself may also address the need for preventive measures for AGS. Figure 18 outlines vaccine approaches and personal protective measures that can be taken to prevent tick-borne disease.

Tick-Borne Disease Treatment

The availability of antimicrobials to treat tick-borne pathogens varies, with established options available for the bacteria and parasites and a dearth of options for the viruses (Table 3). Accelerated research on new antimicrobials across the disease spectrum is therefore needed, with special attention paid to the tick-borne viruses. New treatments for AGS are also needed and should be a priority.

For Lyme disease the question of treatment is more complex, given differing perspectives on the underlying causes of persistent symptoms in some individuals and the appropriate therapeutic approach to preventing or alleviating those symptoms. Research on the underlying pathogenesis of persistent signs and symptoms attributed to Lyme disease remains an unmet need, as are clinical studies built on those discoveries. Federal agencies should encourage studies that directly address gaps in our understanding of Lyme disease treatment, including post-treatment symptoms, pregnancy outcomes, and neuropsychiatric symptoms. Persistence issues should also be addressed for other tick-borne diseases where they have been identified or proposed.

Table 3. Approved Vaccines and Antimicrobials for Tick-borne Diseases

	Antimicrobials	Vaccines
Alpha-gal Syndrome	N/A	No
Babesiosis	Yes	No
Lyme Disease	Yes	No
Rickettsial Diseases	Yes	No
Tick-borne Relapsing Fever	Yes	No
Tick-borne Viruses	No	TBEV only

Chapter 8
Conclusion and Looking Forward

Recommendation 8.1: Request that following sunset of the Tick-Borne Disease Working Group, HHS's Office of the Assistant Secretary for Health (OASH) convene regular virtual public co-creation or collaboration workshops and technical consultations, in concert with relevant HHS operating divisions (CDC, FDA, NIH, and CMS) and with other relevant federal departments to share updates and receive input on progress made towards implementing federal advisory committee (FAC) recommendations from the three reports to Congress. The recommendations should be tracked back to the Goals, Strategies, and Objectives of the anticipated national public health strategy for the prevention and control of vector-borne diseases in humans, of which HHS/OASH is currently leading the development, to ensure progress is made on recommendations, as resources allow. Through these regularly convened public engagement sessions, public input should be collected and an open dialogue should be supported to ensure continued, meaningful engagement with the tick-borne disease community (including patients, advocates, scientists, clinicians, and educators).

Rationale

The current federal advisory committee completed three full report cycles, thus fulfilling the original legislative mandate of the 21st Century Cures Act. From the three formal reports, including the current 2022 report, more than 70 recommendations have been made regarding federal activities that address concerns related to tick-borne disease prevention, control, surveillance, diagnostics, treatment, education, and access to care. Although the Department of Health and Human Services (HHS) Tick-Borne Disease Working Group has been very successful in accomplishing the original mandate and noteworthy progress has been achieved, significant work remains. The need has evolved from assessing federal activities and gaps and making recommendations, to one of effectively implementing the recommendations that have been made to date, which is an operational function of the federal government. To support this function, the need remains for meaningful two-way interaction to prioritize actions, support implementation, and identify barriers to implementation. This work can be most efficiently and effectively achieved through an HHS-led, multi-pronged process as described in the above recommendation.

This is the third and final report of the Tick-Borne Disease Working Group. Over the course its six-year tenure, the advisory committee has included 20 members of the public and 15 representatives of governmental agencies involved in U.S. tick-borne disease efforts. The Working Group has made more than 70 recommendations to Congress (Appendix C. 2018, 2020, 2022 Recommendations of the Tick-Borne Disease Working Group). Action on specific recommendations made in the prior reports have been initiated and include but are not limited to the following:

- Increased funding for systematic studies to identify novel tick-borne disease agents in the United States

- Support of studies on the economic impacts of tick-borne diseases and associated illnesses

- Provision of additional funding for tick control strategies

- Increased educational resources for clinicians and the general public regarding tick-borne diseases through the creation of web-based modules

- Support of new programs to advance development of new diagnostics for Lyme disease and other tick-borne diseases

- Development of educational material for Alpha-gal Syndrome

- Establishment of a national tick surveillance program and a national tick bite data tracker

- Support of new programs to advance research on tick-borne disease prevention, genetic tools for understudied tick-borne pathogens, and persistent symptoms in Lyme disease

- Creation of the NIH Strategic Plan for Tick-Borne Diseases Research

- Streamlining of the surveillance reporting process for Lyme disease to ease the burden on public health departments

- Initial development of a national strategy for vector-borne diseases

- Facilitation of the National Academies multi-stakeholder collaboration to develop a workshop that examines common, overlapping clinical and biological factors underlying infection-associated chronic illness (including Lyme disease, myalgic encephalomyelitis/chronic fatigue syndrome, and long COVID), and related diagnostic tests and therapeutic targets

Despite this progress, much work remains to be done. According to *The 2022 National Inventory of Tick-Borne Diseases and Associated Illnesses*, which includes a review of published and unpublished literature (from January 1, 2018, to June 30, 2022) and a survey of federal agencies, states, and private funding organizations:

> …significant gaps [exist] in research, particularly within disadvantaged groups with elevated risk of acquiring tick-borne diseases and associated illnesses. These groups include those of lower socioeconomic status, regional and rural populations, racial and ethnic minorities, and high-risk outdoor workers. Generalizability was lacking overall with insufficient representation of certain groups within studies and a lack of focus on certain at-risk populations (OIDP, 2022).

Based on the findings of its expert subcommittees, the Working Group has highlighted in the recommendations of this third Report to Congress both emerging areas of need and issues of continued concern. The challenges in addressing the risk to human health that tick-borne diseases present continue to grow. These challenges include introduction of new diseases; changes in climate and environment that allow expansion of ticks into new regions; continued limited understanding of disease pathogenesis, which precludes development of better approaches to diagnosis, treatment, and prevention; and structural barriers to overcoming these limitations. The recommendations from each of the Working Group's three reports lay the groundwork for an effective federal response to the threat of tick-borne diseases and associated illnesses. Looking forward, the implementation of strategies that address these recommendations will be critical to improving the health of the nation.

Minority Response: A Premature Demise?

The Conclusion and Looking Forward chapter of the 2022 Tick-Borne Disease Working Group Report to Congress, which highlights many of the federal actions that have been taken in response to prior Working Group recommendations, makes no mention of the 2022 Working Group's major failing—the decision by the majority to not recommend renewing the Tick-Borne Disease Working Group, which by statute, sunsets in December of 2022. The purpose of this minority report is to demonstrate why that decision is in error and to suggest a way forward.

Generally speaking, federal advisory committees (FACs) serve two important purposes, to provide information and advice that would not otherwise be available through sources internal to the federal government and to provide an opportunity for the public to directly participate in this process (GSA, 2019).

The structure of the Working Group created opportunities for success on both fronts. During its six-year existence, the Working Group drew not only on the expertise of its appointed members, but also on the multitude of subject matter experts, including those from the patient community, who served on 19 of the 21 different subcommittees. The broad spectrum of scientific perspectives and the inclusion of patients and patient representatives allowed for vigorous and respectful debates on highly contentious topics that (a) identified and prioritized gaps in the federal response to the threats posed by tick-borne diseases and conditions, (b) proposed innovative strategies aimed at preventing, diagnosing, and effectively treating them, and (c) fostered relationship building between federal and public members. The benefits of employing this collaborative approach are reflected in the recommendations generated by the 2018, 2020, and 2022 Working Group members.

Progress on implementing these recommendations has been slow and uneven. While Working Group members agreed on the need to transition from identifying and addressing gaps toward implementing the recommendations that have already been made, there was disagreement as to how to proceed. Although there was widespread support at the April 27-28, 2022, meeting for a single FAC that included multiple components, an official vote on the matter was tabled so that a smaller group could work out the details of the recommendation (HHS, 2022). In the months that followed, the federal members' support for the FAC recommendation evaporated, and the FAC recommendation put forth by that smaller group at the October 4-5, 2022, meeting did not pass.

The majority, which included all of the federal members, erroneously maintained that because implementation is operational in nature, it is strictly within the purview of the federal government. Many expressed the belief that renewing the Working Group would place an undue burden, both in time and money, on the agencies. The majority appeared to believe that listening sessions and public workshops will be sufficient means for continuing public engagement.

Those who supported renewing the Working Group respectfully disagree. We recognize that many of the gains the Working Group achieved were largely attributable to its unique ability to bring together disparate perspectives on equal footing. Among the many tick-borne diseases, Lyme disease has been an especially contentious topic for decades (Access to Care Services and Support to Patients Subcommittee, 2018; Maloney, 2016; Tonks, 2007). In their oral and written testimony to the Working Group as well as in a recently circulated petition to members of

this Working Group, the Lyme disease community related how the voices of patients, clinicians, and researchers who challenge prevailing scientific and medical practices, particularly with regard to patients who remain ill after antibiotic treatment, have been systematically marginalized and/or silenced. As described in Chapter 3, Access to Care and Education, these types of structural barriers contribute to the health disparities that plague this patient population.

Other groups within the broader tick-borne disease landscape were also beneficiaries of the Working Group structure. The considerable exposure that the Alpha-gal Syndrome community gained during the first cycle earned it well-deserved attention within all three reports, and in 2022 an entire subcommittee report was devoted to this important medical topic.

For many within the tick-borne disease community, the equality afforded to them by the Working Group structure and processes and the efforts at building consensus were laudable departures from the past. The community response to this successful forum has been to lobby for more tick-borne disease funding for NIH and CDC, and funding for these agencies has increased significantly as a result of these efforts. Discontinuing this forum may adversely affect future patient lobbying efforts as, from their perspective, listening sessions and informational exchanges represent a step backwards, not forwards.

The work needed to achieve health equity for patients with tick-borne illnesses and associated illnesses is far from complete. Given that FACs are routinely renewed when their work is unfinished,

it is a mistake for the majority to abandon this successful approach for engaging patients and soliciting input from a wide range of subject matter experts. Rather, the Working Group should be renewed under a new charter that pivots to building on the work that has already been done. Implementation of Working Group recommendations would benefit from the experiences and knowledge of outside experts and the affected patient groups. This "slimmed down" version of the Working Group would retain the critically important elements discussed above while reducing the financial and time commitments that were concerns to some federal members. Continuing public participation and federal transparency regarding federal tick-borne disease activities will increase the tick-borne disease community's confidence that their needs and concerns are appropriately assessed and addressed.

Recognizing that the vote on the recommendation to continue the Working Group will not be reconsidered, the future of the Tick-Borne Disease Working Group rests in the hands of the tick-borne disease community and their elected representatives. Patients, clinicians, and researchers who want the Working Group to continue should contact their federal representatives and urge them to pass legislation to reinstate the Working Group so that it can continue the work it so ably started.

Respectfully,
Elizabeth Maloney, MD

References

Access to Care Services and Support to Patients Subcommittee (2018). Report to the Tick-Borne Disease Working Group. U.S. Department of Health and Human Services. https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/access-to-care-2018-5-9/index.html

GSA (U.S. General Services Administration). (2019). The Federal Advisory Committee Act (FACA) Brochure. https://www.gsa.gov/policy-regulations/policy/federal-advisory-committee-management/advice-and-guidance/the-federal-advisory-committee-act-faca-brochure

HHS (U.S. Department of Health and Human Services). (2022, April 29). Tick-Borne Disease Working Group Meeting | April 27 – 28, 2022 | Day 2, Part 1. YouTube. https://www.youtube.com/watch?v=sxkU_jYJFRU

Maloney, E. L. (2016). Controversies in persistent (chronic) Lyme disease. *Journal of Infusion Nursing: The Official Publication of the Infusion Nurses Society, 39*(6), 369–375. https://doi.org/10.1097/NAN.0000000000000195

Tonks, A. (2007). Lyme wars. BMJ, 335, 910–912. https://doi.org/10.1136/bmj.39363.530961.AD

Core Values to Achieve One Shared Vision

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

RESPECT:
Everyone is valued

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

INNOVATION:
Shifting the paradigm, finding a better way

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

HONESTY & INTEGRITY:
Find the truth, tell the truth

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

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

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

COMPASSION:
Finding solutions to relieve suffering

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

COLLABORATION:
Work with citizens and patients as partners

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

ACCOUNTABILITY:
The buck stops here

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

Appendices

Appendix A: Tick-Borne Disease Working Group

Holiday Goodreau (Co-Chair)
Public member category: Patient advocate and family member
Executive Director, LivLyme Foundation; Co-creator, TickTracker

Linden Hu, MD (Co-Chair)
Public member category: Physician
Professor of Microbiology and Medicine, Vice Dean for Research, Tufts University School of Medicine

Charles Benjamin (Ben) Beard, PhD
Deputy Director, Division of Vector-borne Diseases, Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services

CAPT Rebecca Bunnell, MPAS, PA-C
Senior Advisor, Learning and Diffusion Group, Center for Medicare & Medicaid Innovation, Centers for
Medicare & Medicaid Services, U.S. Department of Health and Human Services

Dennis Dixon, PhD
Chief, Bacteriology and Mycology Branch, National Institute of Allergy and Infectious Diseases, National
Institutes of Health, U.S. Department of Health and Human Services

Monica E. Embers, PhD
Public member category: Researcher
Associate Professor and Director, Vector-borne Disease Research, Tulane National Primate Research Center

Elizabeth Maloney, MD
Public member category: Patient advocate
President, Partnership for Tick-borne Diseases Education

Robert J. Miller, PhD
National Program Leader, Agricultural Research Service, U.S. Department of Agriculture

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

Jennifer Platt, DrPH
Public member category: Patient and patient advocate
Co-founder, Tick-borne Conditions United

Sunil K. Sood, MD
Public member category: Physician
Chair of Pediatrics, South Shore University Hospital; Attending Physician, Infectious Diseases, Cohen Children's
Medical Center; Professor of Pediatrics, Hofstra/Northwell

Kirby C. Stafford III, PhD
Public member category: Researcher
Chief Scientist and State Entomologist, Department of Entomology, Center for Vector Biology & Zoonotic Diseases, The Connecticut Agricultural Experiment Station

Leith Jason States, MD, MPH (FMF)
Deputy Chief Medical Officer, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Gabriella Zollner (Romero), PhD
Program Manager, Deployed Warfighter Protection Program, U.S. Department of Defense

Designated Federal Officers

James (Jim) Berger, MS, MT (ASCP) SBB, (Designated Federal Officer)
Senior Blood and Tissue Policy Advisor, Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

B. Kaye Hayes, MPA, (Alternate Designated Federal Officer)
Deputy Assistant Secretary, Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Support Staff

Chinedu Okeke, MD, MPH-TM, MPA
Senior Policy Advisor, Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Lauren Overman, MPH, CPH
Public Health Analyst, Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Allison Petkoff
Public Health Analyst, Office of Infectious Disease and HIV/AIDS Policy, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Contractor

Rose Li & Associates, Inc.

Appendix B: Tick-Borne Disease Working Group Subcommittees

All subcommittees were overseen by the Working Group Co-Chairs:

Holiday Goodreau
Executive Director, LivLyme Foundation; Co-creator, TickTracker

Linden Hu, MD
Professor of Microbiology and Medicine, Vice Dean for Research, Tufts University School of Medicine

Access to Care and Education

CAPT Rebecca Bunnell, MPAS, PA-C (Co-Chair)
Senior Advisor, Learning and Diffusion Group, Center for Medicare & Medicaid Innovation, Centers for Medicare & Medicaid Services, U.S. Department of Health and Human Services

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

Holly Ahern, MS, MT(ASCP)
Associate Professor of Microbiology, SUNY Adirondack

Megan DuLaney, MS
Senior Advisor, U.S. Department of State

Lorraine Johnson, JD, MBA
Chief Executive Officer, MyLyme.Org

David Roberts, MD
Associate Professor of Medicine, Dean for External Education, Harvard Medical School

Ginger Savely, DNP
Provider Specializing in the Treatment of Lyme Disease; Speaker and Author with a Focus on Lyme Disease

Leith Jason States, MD, MPH (FMF)
Chief Medical Officer, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Beatrice Szantyr, MD
Physical Educator on Lyme Disease and Other Tick-Borne Diseases

Changing Dynamics of Tick Ecology, Personal Protection, and Control

Robert J. Miller, PhD (Co-Chair)
National Program Leader, Agricultural Research Service, U.S. Department of Agriculture

Kirby C. Stafford III, PhD (Co-Chair)
Chief Scientist and State Entomologist, Department of Entomology, Center for Vector Biology & Zoonotic Diseases, The Connecticut Agricultural Experiment Station

Jill Auerbach
Chairperson, Hudson Valley Lyme Disease Association; Coordinator, Tick Research to Eliminate Diseases: Scientist Coalition

Lars Eisen, PhD
Research Entomologist, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic
Infectious Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

Amanda Elam, PhD
President/CEO, Galaxy Diagnostics

Dina Fonseca, PhD
Professor and Director, Center for Vector Biology, Rutgers University, The State University of New Jersey

Rebecca Trout Fryxell, PhD
Associate Professor, Medical and Veterinary Entomology, The University of Tennessee Institute of Agriculture

Holly Gaff, PhD
Professor, Department of Biological Sciences, Old Dominion University

Erika T. Machtinger, PhD
Assistant Professor of Entomology, College of Agricultural Science, The Pennsylvania State University

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

Daniel Salkeld, PhD
Research Scientist, Department of Biology, Colorado State University

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

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

Clinical Presentation and Pathogenesis

Charles Benjamin (Ben) Beard, PhD (Co-Chair)
Deputy Director, Division of Vector-borne Diseases, Centers for Disease Control and Prevention, U.S.
Department of Health and Human Services Meghan Bradshaw
Patient Advocate

Jennifer Platt, DrPH, MSPH (Co-Chair)
Co-founder, Tick-borne Conditions United

Leith Jason States, MD, MPH (FMF) (Co-Chair)
Chief Medical Officer, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services

Meghan Bradshaw
Patient Advocate

Sue Faber, RN, BScN
Co-founder, LymeHope

Brian Fallon, MD, MPH
Director, Lyme and Tick-Borne Diseases Research Center, Columbia University Irving Medical Center

Allison Hinckley, PhD
Epidemiology Team Lead, Bacterial Diseases Branch, Division of Vector-borne Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

Jacob Lemieux, MD, PhD
Clinical Researcher, Massachusetts General Hospital

Tina Merritt, MD
Healthcare Provider Specializing in Alpha-gal Syndrome

Rhisa Parera
Tick-borne Disease Patient and Advocate

Diagnostics

Monica E. Embers, PhD (Co-Chair)
Associate Professor of Microbiology and Immunology and Director, Vector-Borne Disease Research, Tulane National Primate Research Center

CDR Todd Myers, PhD, HCLD (Co-Chair)
Office of Counterterrorism and Emerging Threats, Office of the Chief Scientist, Office of the Commissioner, U.S. Food and Drug Administration, U.S. Department of Health and Human Services

John Aucott, MD
Director, Johns Hopkins Lyme Disease Clinical Research Center; Associate Professor of Medicine, Johns Hopkins Medicine

John Belisle, PhD
Professor, Co-Director, Center for Metabolism and Infectious Diseases, Colorado State University

John Branda, MD
Associate Professor of Pathology, Harvard Medical School; Associate Director, Microbiology Laboratory, Massachusetts General Hospital

Tammy Crawfod
Founder, Executive Director, Focus on Lyme

Amanda Elam, PhD
CEO/Cofounder, Galaxy Diagnostics

Liz Horn, PhD, MBI
Principal Investigator, Lyme Disease Biobank, LHC BioSolutions

Robyn Nadolny, PhD
Chief, Molecular Biology Section and Tick-Borne Disease Laboratory, Laboratory Sciences Directorate, U.S. Army Public Health Center

Rafal Tokarz, PhD
Assistant Professor of Epidemiology, Center for Infection and Immunity, Columbia University Medical

Disease Prevention and Treatment

Dennis Dixon, PhD (Co-Chair)
Chief, Bacteriology and Mycology Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services

Sunil Sood, MD (Co-Chair)
Chair of Pediatrics, South Shore University Hospital; Attending Physician, Infectious Diseases, Cohen Children's Medical Center; Professor of Pediatrics, Hofstra/Northwell

Scott P. Commins, MD, PhD
Associate Professor, Section Chief, Allergy & Immunology, University of North Carolina School of Medicine

Gregory Ebel, ScD
Professor, Colorado State University

Erol Fikrig, MD
Professor of Medicine, Epidemiology, and Microbial Pathogenesis, Yale Institute for Global Health; Section Chief, Infectious Diseases

Tony Galbo
Patient Advocate and Family Member

Peter J. Krause, MD
Senior Research Scientist, Department of Epidemiology (Microbial Diseases), Yale School of Public Health

Charlotte Mao, MD, MPH
Researcher and Physician, Dean Center for Tick Borne Illness, Spaulding Rehabilitation Hospital

Luis A. Marcos, MD, MPH
Director, Infectious Diseases Fellowship Program, Stony Brook University; Associate Professor of Medicine, Microbiology and Immunology, Stony Brook University Health Sciences Center School of Medicine

Paul Mead, MD, MPH
Chief, Bacterial Diseases Branch, Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

Christopher Paddock, MD, MPHTM
Pathology, Rickettsia Zoonoses Branch, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services

Sam Perdue, PhD
Section Chief, Basic Sciences and Officer, Rickettsia and Related Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services

Mark Soloski, PhD
Professor of Medicine, Johns Hopkins University School of Medicine; Advisor, Johns Hopkins Lyme Disease Research Center

Charlie Stockman
Lyme Disease Patient

Appendix C: 2018, 2020, and 2022 Recommendations of the Tick-Borne Disease Working Group

2018 Recommendations

Chapter 3: Epidemiology and Ecology

Recommendation 3.1: 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.

Recommendation 3.2: Fund systematic studies and activities to identify and characterize novel tick-borne disease agents in the United States.

Recommendation 3.3: 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.

Recommendation 3.4: Have public health authorities formally recognize complementary, 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.

Recommendation 3.5: 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).

Chapter 4: Prevention

Recommendation 4.1: 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 4.2: 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 4.3: 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 4.4: Prioritize education by informing clinicians and the general public about the regional and specific risks related to tick-borne diseases.

Chapter 5: Diagnosis

Recommendation 5.1: Evaluate new technology or approaches for the diagnosis of Lyme disease and other tick-borne diseases.

Recommendation 5.2: Include special populations, especially children, in Lyme disease and other tick-borne diseases diagnostic studies.

Chapter 6: Treatment

Recommendation 6.1: 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 6.2: 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 6.3: 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 6.4: Conduct additional clinical trials appropriate to the target populations where gaps may exist.

Recommendation 6.5: Improve the education and research on the pathogenesis of alpha-gal allergy, also known as the tick-caused "meat allergy."

Chapter 7: Access to Care, Patients Outcomes

Recommendation 7.1: Create a Federal repository for information on Lyme disease and other tick-borne diseases.

Recommendation 7.2: Allocate increased funding for tick-borne disease in the areas of research, treatment, and prevention proportional to the burden of illness and need.

Recommendations: 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 7.3:** Protect patients from employment discrimination.

- **Recommendation 7.4:** Protect students of all ages from discrimination.

- **Recommendation 7.5:** Protect patients from health care and disability insurance coverage and reimbursement policies that are unduly burdensome.

- **Recommendation 7.6:** 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.

Chapter 8: Looking Forward

Recommendation 8.1: 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 tick-borne diseases. Update every five years.

Recommendation 8.2: 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 tickborne disease patients with continuing manifestations of disease after initial treatment.

Recommendation 8.3: 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 8.4: VA: Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members.

Recommendation 8.5: 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.

2020 Recommendations

Chapter 3: Tick Biology, Ecology, and Control

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

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

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

Chapter 4: Clinical Manifestations, Diagnosis, and Diagnostics

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

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

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

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

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

Chapter 5: Causes, Pathogenesis, and Pathophysiology

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

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

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

Chapter 6: Treatment

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

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

Chapter 7: Clinical and Public Education, Patient Access to Care

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

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

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

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

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

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

Chapter 8: Epidemiology and Surveillance

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

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

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

Chapter 9: Federal Inventory

Recommendation 9.1: VA: Recommend that the VA continue with Recommendation 8.4 from 2018 Working

Group report, "Commence study of tick-borne disease incidence and prevalence of Veterans and eligible family members" and additionally

- Establish and update efforts on tracking and investigating the prevalence of Lyme and other tick-borne diseases; and

- Make educational modules available to practitioners.

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

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

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

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

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

- Reimbursement costs for the diagnosis and treatment of beneficiaries with Lyme disease and other tick-borne diseases;

- Demonstration and pilot projects with Lyme disease and other tick-borne diseases as their focus; and

- Quality measure development and implementation related to Lyme disease and other tick-borne diseases.

2022 Recommendations

Chapter 3: Access to Care and Education

Recommendation 3.1: Provide funding for the U.S. Department of Health and Human Services to sponsor the National Academy of Medicine (NAM) within the National Academies of Science, Engineering and Medicine to conduct an objective, comprehensive review of the basic science and clinical evidence for diagnosis and treatment of Lyme disease, with emphasis on acute and Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD). The purpose for conducting an objective review would be to establish what is definitely known, what is partially understood, and what remains unknown about Lyme disease. The review mechanism shall be transparent and include public stakeholders and patient representatives, experts in trial design and execution, as well as a diversity of experts who represent the full spectrum of scientific perspectives on Lyme disease. The expert panel will produce a comprehensive public report, which will be used to inform federal and state initiatives.

Recommendation 3.2: Upon activation of Recommendation 8.1 of the Tick-Borne Disease Working Group 2022 Report to Congress outlining implementation of Working Group priorities, the first recommendations to be discussed for updates and public input are Recommendations 7.1 and 7.2 from the Tick-Borne Disease Working Group 2020 Report to Congress that address educational materials and web content. Emphasis should

be placed on receiving input via meaningful engagement with stakeholders on how these recommendations have been implemented to date across HHS operating divisions and how well they reflect the current state of the science.

Recommendation 3.3: Fund and support continued and ongoing modification of the federal government websites, starting with the CDC and NIH websites, as well as educational materials and seminars for clinicians, the public, and public health departments to reflect the current state of the science related to Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD), which is limited, emerging, and unsettled, and to acknowledge that there are divergent views on diagnosis and treatment of patients with PLD/CLD.

Recommendation 3.4: Provide the HHS Secretary with discretionary authority to maintain telehealth flexibilities independent of Public Health Emergency declaration for patients with tick-associated illnesses in order to ensure access, parity, and equity for those receiving in-person and telehealth services.

Recommendation 3.5: Fund, support, and encourage community-based participatory research programs for Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD) and complex presentations of late Lyme disease and other tick bite-associated illnesses. This includes the development and growth of community research capacity to accelerate the fundamental knowledge base using "big data" registries, data-sharing platforms, specimen and tissue sample repositories, and genomic and precision medicine approaches that reflect the underlying heterogeneous nature of tick-borne diseases and associated illnesses.

Chapter 4: Changing Dynamics of Tick Ecology, Personal Protection, and Control

Recommendation 4.1: Increase funding for research on tick ecology towards more effective tick and tick-borne disease surveillance and tick control. Tick ecology is an important part of the One Health concept that also includes people and companion animals.

Recommendation 4.2: Increase funding to develop, evaluate, and deploy tick bite prevention and tick control approaches and strategies. Minimize roadblocks and streamline the regulatory process for getting new tick bite prevention and tick control products to market.

Recommendation 4.3: Increase adoption and expand knowledge of tick bite prevention and tick control methods across all affected groups, including implementation of occupational standards for employees at high risk of tick-associated illnesses.

Chapter 5: Clinical Presentation and Pathogenesis

Recommendation 5.1: Support additional research on the mechanisms of pathogenesis of tick-borne disease, with a particular focus on central nervous system infection (including neuropsychiatric illness and neuropathic injury), persistent symptoms, allergy (Alpha-gal Syndrome), immunity, autoimmunity, pregnancy, and adverse fetal outcomes.

Recommendation 5.2: Provide funding to support research investigating the prevalence of undetected tick-borne illness among subgroups of the population who may have multi-systemic chronic conditions (e.g., mental illness, musculoskeletal diseases, etc.) and who have been inadequately medically evaluated, including individuals in psychiatric facilities, prisons, homeless shelters, other populations experiencing health disparities or disabilities.

Recommendation 5.3: Require labeling of foods, products, beverages (including alcohol), cosmetics, and pharmaceuticals that contain non-primate mammalian ingredients (active or inactive) and update the FDA's Food Safety Modernization Act to incorporate Alpha-gal Syndrome (AGS) awareness training into the FDA's "Retail Food Industry/Regulatory Assistance and Training" Program.

Recommendation 5.4: Provide funding for studies, particularly prospective studies, that evaluate clinical similarities, mechanisms of pathogenesis, and common etiologies for long COVID and other infection-associated chronic illnesses, with tick-associated chronic illness and/or persistent symptoms associated with tick-borne diseases.

Recommendation 5.5: Develop and maintain comprehensive biospecimen repositories (e.g., whole blood, sera, cerebrospinal fluid, maternal and fetal tissues and fluids, and autopsy specimens) for use in developing and/or improving diagnostic assays, both direct and indirect, and for research into transmission and pathogenesis, for broad applications including early diagnosis, distinction of current versus past infection, and for use in pregnancy and fetal outcome applications.

Chapter 6: Diagnostics

Recommendation 6.1: Convene a panel of stakeholders and experts in tick-borne disease diagnostics, including but not limited to researchers, government, investors, small businesses, large clinical labs, patient advocates, and diagnostics companies, with the goal of promoting the evaluation and development of current and promising new diagnostic approaches.

Recommendation 6.2: Recommend increases in federal funding (CDC or NIH) to: (1) build a national biorepository of human clinical specimens for tick-borne disease supported by a national network of qualified labs and physician clinics; and (2) build a clinical and translational research program involving a network of clinical and academic centers.

Recommendation 6.3: Provide federal support for tick-borne-disease diagnostics through an innovation pipeline with direct Congressional appropriations for a tick-borne-disease innovation accelerator and system that provides targeted funding opportunities, use authorization, lab-to-market commercialization, and implementation via relevant federal agencies.

Chapter 7: Disease Prevention and Treatment

Recommendation 7.1: Improve the quality, timeliness, and completeness of surveillance and reporting of tick-borne diseases nationwide. The resulting information should be used to educate health care providers and the public to prevent, diagnose, and treat tick-borne diseases.

Recommendation 7.2: Increase funding to develop multi-pathogen vaccines, "anti-tick" vaccines, and new prevention strategies to provide broad protection against different tick-borne pathogens. Research on stand-alone Lyme disease vaccines should look for alternatives to human OspA-based vaccine approaches.

Recommendation 7.3: Accelerate discovery, preclinical and clinical development of effective treatments for tick-borne diseases. Increase funding for research into understudied areas of treatment for tick-borne diseases, including but not limited to pediatric neuropsychiatric illnesses, pregnancy outcomes in infected women, and persistent post-treatment symptoms in all age groups, with emphasis on Lyme disease.

Chapter 8: Conclusion and Looking Forward

Recommendation 8.1: Request that following sunset of the Tick-Borne Disease Working Group, HHS's Office of the Assistant Secretary for Health (OASH) convene regular virtual public co-creation or collaboration workshops and technical consultations, in concert with relevant HHS operating divisions (CDC, FDA, NIH, and CMS) and with other relevant federal departments to share updates and receive input on progress made towards implementing federal advisory committee (FAC) recommendations from the three reports to Congress. The recommendations should be tracked back to the Goals, Strategies, and Objectives of the anticipated national public health strategy for the prevention and control of vector-borne diseases in humans, of which HHS/OASH is currently leading the development, to ensure progress is made on recommendations, as resources allow. Through these regularly convened public engagement sessions, public input should be collected and an open dialogue should be supported to ensure continued, meaningful engagement with the tickborne disease community (including patients, advocates, scientists, clinicians, and educators).

Appendix D: Methods of the Working Group

The Tick-Borne Disease Working Group utilized five subcommittee reports, public comments, and both published and unpublished research to inform the Tick-Borne Disease Working Group 2022 Report to Congress. A complementary report—*The 2022 National Inventory of Tick-Borne Diseases and Associated Illnesses*—was also prepared for the Working Group to provide insight into the current national response to tick-borne diseases and associated illnesses and to identify gaps. This section describes the Working Group's subcommittees and how their work informed the Report to Congress, minority responses, the process for receiving and reviewing public comments, and the components of the National Inventory.

Subcommittees and Report Development

In August 2021, the Working Group established the following five subcommittees composed of qualified and experienced members to gather information, data, and research that would enable the Working Group to thoroughly examine several issues related to tick-borne diseases and associated illnesses.

- Access to Care and Education
- Clinical Presentation and Pathogenesis
- Diagnostics
- Disease Prevention and Treatment
- Public Comments
- Tick Ecology, Personal Protection, and Control

Each subcommittee consisted of 9 to 14 individuals with diverse perspectives, trainings, and experiences, including at least one patient or patient advocate. Working Group members served as subcommittee co-chairs, responsible for recruiting members, organizing speaker schedules, and assigning writing tasks. Each subcommittee had at least one federal and one public Working Group member. To facilitate cohesion and communication among the groups, one or both of the Working Group's Co-Chairs attended most subcommittee meetings. They also attended weekly status meetings with the Designated Federal Officer and support staff to track and monitor subcommittee progress.

Over a four-month period, weekly or biweekly subcommittee meetings offered opportunities for open dialogue and presentations from subject matter experts.[3] Each subcommittee identified several priorities, divided into writing groups, and developed a report to the Working Group that described current efforts, gaps in research, and potential actions to address each priority. In drafting their reports, the subcommittees compiled information from expert, advocate, and patient presentations; collective subcommittee member knowledge; and literature reviews. In finalizing their reports, subcommittee members voted on the priority findings. During Public Meeting 20 (February 28 and March 1, 2022), each subcommittee's co-chairs presented their findings to the Working Group. They gave a slide presentation highlighting their respective report's background, methods, findings, and rationale. All subcommittee reports are available on the Working Group's website.

In the following months, the Working Group prioritized and revised the subcommittees' findings to generate and vote on recommendations for the 2022 Report to Congress. Members formed writing groups, which drew from the subcommittee reports and public comments to develop chapter content. After all members had the opportunity to review draft material, provide input, and read revisions, the Working Group voted on individual chapters and the report in its entirety.

---

[3]The subcommittees were established to conduct preparatory work for the Working Group to consider, and their work process differed from that of the Working Group. For example, the subcommittees were not required to follow the same FACA requirements (41 C.F.R. § 102–3.35; 41 C.F.R. at § 102–3.160(a)).

In addition to the five subcommittees described previously, the Working Group continued the Public Comment Subcommittee, composed of four Working Group members. Originally formed during the 2020 cycle, this subcommittee continued the work of processing and synthesizing input received from members of the public.

Minority Responses

Some of the content in this report is subject to opposing viewpoints. These are expressed in a minority response at the end of Chapter 8: Conclusion and Looking Forward. The minority response reflects the views of the individual author and not necessarily the views of the Working Group or the U.S. Department of Health and Human Services.

Public Input

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

- **Verbal comments given at Working Group public meetings**

  Every Working Group meeting allocated time for public comments. A three-minute time limit was instituted for each commenter to allow as many members of the public to participate as possible.

- **Written comments submitted prior to the Working Group public meetings**

  To accommodate individuals who could not attend the public meetings, the public was invited to submit their written comments to the Working Group. Comments received for all meetings can be viewed in each meeting tab on the Working Group's website.

- **Email comments**

  The public could also email their comments to the Working Group. Emails were reviewed but not published on the Working Group website. Emails received on or before October 11, 2022, were reviewed and considered in this report. Those received on or after October 12, 2022, were reviewed but not incorporated into the report.

All Working Group members received every public comment via Word documents. In addition, the Public Comments Subcommittee synthesized public input and presented key themes at public meetings. The results of the subcommittee's work are summarized in Chapter 2: Public Comments.

The *2022 National Inventory of Tick-Borne Diseases and Associated Illnesses*

The 2018 and 2020 Federal Inventories were developed to collect and synthesize information from federal agencies regarding research and surveillance of tick-borne diseases. The survey data were used to inform the Working Group about advances, overlaps, and gaps in federal activities. This year the inventory was expanded into the *2022 National Inventory of Tick-Borne Diseases and Associated Illnesses*, comprising two data collection methods:

- A scoping review of published and unpublished literature
- A survey of five federal agencies, five states, and seven private organizations

The National Inventory was designed to provide a comprehensive overview of the national response to tick-borne diseases and associated illnesses with the aim of establishing a baseline of data and a reliable framework from which to build future tick-borne disease inventories.

Scoping Review of Literature

The scoping review is an assessment of the compilation of human tick-borne disease research, both published and unpublished, in the United States between January 1, 2018, and June 30, 2022. The review included national research related to causes, prevention, treatment, surveillance, diagnosis, diagnostics, duration of illness, and clinical presentation and pathogenesis of tick-borne diseases and associated illnesses. The goal was to examine the extent, range, and nature of research activities, identify research gaps and overlaps, and summarize and disseminate research findings.

Survey of Federal Agencies, States, and Private Organizations

The survey component characterizes devoted tick-borne disease staffing, funding, and related activities across federal agencies, states, and private organizations in areas of research, programs, and public health initiatives since 2018. Federal survey responses were received from the Centers for Disease Control and Prevention, National Institutes of Health, Food and Drug Administration, Department of Defense, and Department of Agriculture. Although the Centers for Medicare & Medicaid Services (CMS) did not participate, a CMS data collection framework was developed to enable a future collection of Medicare reimbursement costs for tick-borne diseases.

Nine states—Connecticut, Delaware, Maine, Minnesota, New Jersey, New York, Pennsylvania, Virginia, and Wisconsin—with the highest incidence of tick-borne diseases were surveyed to determine the activities and expenditures on tick-borne diseases per year, from 2018 to 2021. Five states provided responses. To augment state data, additional sources of state data were collected and included in the National Inventory. These included the 2020 Vector Control Assessment, conducted by the National Association of Country and City Health Officials (NACCHO), and annual published state reports.

Eight U.S.-based, private organizations that provide funding for tick-borne disease research or programs were also surveyed, with seven respondents. These organizations were identified by soliciting names of the top funders from 2022 Working Group members. Survey respondents provided information about the types of activities and research they fund, public-private sector collaborations, and public engagement.

Appendix E: Acronyms and Abbreviations

AGS	Alpha-gal Syndrome
ARPA-H	Advanced Research Project Agency for Health
BARDA	Biomedical Advanced Research and Development Authority
CBPR	community-based participatory research
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CME	continuing medical education
CMS	Centers for Medicare & Medicaid Services
CPG	clinical practice guideline
CSTE	Council of State and Territorial Epidemiologists
DARPA	Defense Advanced Research Projects Agency
ddPCR	droplet digital polymerase chain reaction
DFO	Designated Federal Officer
DoD	U.S. Department of Defense
ELISA	enzyme-linked immunosorbent assay
EM	erythema migrans
FAC	federal advisory committee
FACA	Federal Advisory Committee Act
FDA	U.S. Food and Drug Administration
FY	fiscal year
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HHS	U.S. Department of Health and Human Services
HRTV	Heartland virus
IgG	immunoglobulin G antibodies
IgM	immunoglobulin M antibodies
mAb	monoclonal antibody
MMWR	Morbidity and Mortality Weekly Report
mRNA	messenger RNA
MTTT	modified two-tier test
NAAT	nucleic acid amplification test
NAM	National Academy of Medicine (formerly Institute of Medicine)
NGS	next-generation sequencing
NIH	National Institutes of Health

OASH	Office of the Assistant Secretary for Health (HHS)
OIDP	Office of Infectious Disease and HIV/AIDS Policy (HHS)
OspA	outer surface protein A
PCR	polymerase chain reaction
PLD/CLD	Persistent Lyme Disease/Chronic Lyme Disease
POWV	Powassan virus
PTLD	Post-treatment Lyme disease
RMSF	Rocky Mountain spotted fever
SAAT	Soliman Auricular Acupuncture Treatment
SARS CoV-2	COVID-19 coronavirus
SDOH	social determinants of health
SLICE	Study of Lyme Disease Immunology and Clinical Events
SNP	single nucleotide polymorphism
STARI	Southern tick-associated rash illness
STTT	Standard two-tier test
TBE	tick-borne encephalitis
TBRF	tick-borne relapsing fever
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
VALID Act	Verifying Accurate, Leading-edge IVCT Development Act

Appendix F: 21st Century Cures Act

The 21st Century Cures Act, enacted in December 2016, authorizes the Secretary of the U.S. Department of Health and Human Services (HHS) to establish a Tick-Borne Disease Working Group to serve as a Federal Advisory Committee. The Working Group is to comprise federal and public members with diverse disciplines and views pertaining to tick-borne diseases. The Act charges the Working Group to provide a report to Congress and the HHS Secretary on its findings and any recommendations every two years. Working Group responsibilities include a review of ongoing research and resulting advances; federal epidemiological and research efforts; and identification of research gaps. The 21st Century Cures Act, Section 2062 Tick-Borne Diseases, is provided below. The legislation is available in its entirety at 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 tickborne diseases.

      (ii) Scientists or researchers with expertise.

      (iii) Patients and their family members.

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

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

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

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

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

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

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

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

Appendix G: Charter of the Tick-Borne Disease Working Group

Charter

The charter defines how the Working Group is structured and functions in response to the charge provided by the 21st Century Cures Act, and is renewed every two years in accordance with federal advisory committee guidelines. The current charter expires August 10, 2023.

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, Public Law 114-255. 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 2).

Objectives and Scope of Activities

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

Description of Duties

The Working Group shall have the following responsibilities:

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

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

  (2) advances made pursuant to such research;

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

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

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

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

  (5) the Working Group's meetings; and

  (6) the comments received by the Working Group.

(B) Make recommendations to the Secretary regarding any appropriate changes or improvements 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 provides 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 activities are provided by the Office of Infectious Disease and HIV/AIDS Policy, which is a program office within the Office of the Assistant Secretary for Health (OASH) 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 $410,728. Estimated person years of staff support required is 2.0, at an estimated annual cost of $189,272.

Designated Federal Officer (DFO)

The Assistant Secretary for Health (ASH) will select the Designated Federal Officer (DFO) from among full-time or permanent part-time staff within OASH, who has 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 as the DFO 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 or Alternate DFO 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 videoconference 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

The duration of the advisory committee is continuing, subject to the Termination section below.

Termination

The 21st Century Cures Act, Section 2062, paragraph (c)7, explains that the Working Group shall terminate on December 13, 2022, which is 6 years after the enactment of the 21st Century Cures Act.

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 members. The seven federal members consist of one or more representatives of each of the following: OASH, the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health; other agencies and offices of the Department of Health and Human Services as the Secretary determines appropriate. The seven non-federal members 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 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 members will be classified as special government employees.

The federal members will be appointed to serve for the duration of time that the Working Group is authorized to operate. Respective agency heads will have discretion on which federal member of their agency will serve as their representative on the Working Group. The non-federal members may be invited to serve as special government employees for overlapping terms of up to four years. Any non-federal 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 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 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 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:

July 29, 2021

Xavier Becerra

Secretary of Health and Human Services

Filing Date:

August 10, 2021

Appendix H: References

AACC. (2019, October 1). FDA clears Lyme disease tests that upend two-tier approach. https://www.aacc.org/cln/articles/2019/october/fda-clears-lyme-disease-tests-that-upend-two-tier-approach

Access to Care Services and Support to Patients Subcommittee. (2018). *Report to the Tick-Borne Disease Working Group*. U.S. Department of Health and Human Services. https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/access-to-care-2018-5-9/index.html

Adrion, E. R., Aucott, J., Lemke, K. W., & Weiner, J. P. (2015). Health care costs, utilization and patterns of care following Lyme disease. *PloS One, 10*(2), e0116767. https://doi.org/10.1371/journal.pone.0116767

Aguero-Rosenfeld, M. E., Nowakowski, J., Bittker, S., Cooper, D., Nadelman, R. B., & Wormser, G. P. (1996). Evolution of the serologic response to Borrelia burgdorferi in treated patients with culture-confirmed erythema migrans. *Journal of Clinical Microbiology*, *34*(1), 1–9. https://doi.org/10.1128/jcm.34.1.1-9.1996

American Medical Association. (2018). Plan for continued progress toward health equity (Resolution 601- A-17). https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-bot33.pdf

Anvari, S., Miller, J., Yeh, C. Y., & Davis, C. M. (2019). IgE-mediated food allergy. *Clinical Reviews in Allergy & Immunology*, *57*(2), 244–260. https://doi.org/10.1007/s12016-018-8710-3

Aucott, J. N., Soloski, M. J., Rebman, A. W., Crowder, L. A., Lahey, L. J., Wagner, C. A., Robinson, W. H., & Bechtold, K. T. (2016). CCL19 as a chemokine risk factor for posttreatment Lyme disease syndrome: A prospective clinical cohort study. *Clinical and Vaccine Immunology: CVI*, *23*(9), 757–766. https://doi.org/10.1128/CVI.00071-16

Aucott, J. N., Yang, T., Yoon, I., Powell, D., Geller, S. A., & Rebman, A. W. (2022). Risk of post-treatment Lyme disease in patients with ideally-treated early Lyme disease: A prospective cohort study. *International Journal of Infectious Diseases*, *116*, 230–237. https://doi.org/10.1016/j.ijid.2022.01.033

Ballreich, J. M., Gross, C. P., Powe, N. R., & Anderson, G. F. (2021). Allocation of National Institutes of Health funding by disease category in 2008 and 2019. *JAMA Network Open*, *4*(1), e2034890. https://doi.org/10.1001/jamanetworkopen.2020.34890

Barthold, S. W., Hodzic, E., Imai, D. M., Feng, S., Yang, X., & Luft, B. J. (2010). Ineffectiveness of tigecycline against persistent *Borrelia burgdorferi*. *Antimicrobial Agents and Chemotherapy*, *54*(2), 643–651. https://doi.org/10.1128/AAC.00788-09

Beard, C. B., Eisen, L., & Eisen, R. J. (2021). The rise of ticks and tickborne diseases in the United States— introduction. *Journal of Medical Entomology, 58*(4), 1487–1489. https://doi.org/10.1093/jme/tjab064

Beard, C. B., Visser, S. N., & Petersen, L. R. (2019). The need for a national strategy to address vector-borne disease threats in the United States. *Journal of Medical Entomology*, *56*(5), 1199–1203. https://doi.org/10.1093/jme/tjz074

Beard, T. R., Ford, G. S., Koutsky, T. M., & Spiwak, L. J. (2009). A valley of death in the innovation sequence: An economic investigation. *Research Evaluation, 18*(5), 343–356. https://doi.org/10.3152/095820209X481057

Bendiscioli, S. (2019). The troubles with peer review for allocating research funding: Funders need to experiment with versions of peer review and decision-making. *EMBO Reports*, *20*(12), e49472. https://doi.org/10.15252/embr.201949472

Berende, A., ter Hofstede, H. J., Donders, A. R., van Middendorp, H., Kessels, R. P., Adang, E. M., Vos, F. J., Evers, A. W., & Kullberg, B. J. (2014). Persistent Lyme Empiric Antibiotic Study Europe (PLEASE)--design of a randomized controlled trial of prolonged antibiotic treatment in patients with persistent symptoms attributed to Lyme borreliosis. *BMC Infectious Diseases, 14,* 543. https://doi.org/10.1186/s12879-014-0543-y

Berghoff W. (2012). Chronic Lyme disease and co-infections: Differential diagnosis. *The Open Neurology Journal*, *6*, 158–178. https://doi.org/10.2174/1874205X01206010158

Bernal, M., Huecker, M., Shreffler, J., Mittel, O., Mittel, J., & Soliman, N. (2021). Successful treatment for alpha gal mammal product allergy using auricular acupuncture: A case series. *Medical Acupuncture*, *33*(5), 343–348. https://doi.org/10.1089/acu.2021.0010

Binder, A. M., Cherry-Brown, D., Biggerstaff, B. J., Jones, E. S., Amelio, C. L., Beard, C. B., Petersen, L. R., Kersh, G. J., Commins, S. P., & Armstrong, P. A. (2022). Clinical and laboratory features of patients diagnosed with alpha-gal syndrome-2010-2019. *Allergy*, 10.1111/all.15539. Advance online publication. https://doi.org/10.1111/all.15539

Binder, A. M., Commins, S. P., Altrich, M. L., Wachs, T., Biggerstaff, B. J., Beard, C. B., Petersen, L. R., Kersh, G. J., & Armstrong, P. A. (2021). Diagnostic testing for galactose-alpha-1,3-galactose, United States, 2010 to 2018. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*, *126*(4), 411–416.e1. https://doi.org/10.1016/j.anai.2020.12.019

Bloemer, S. R., Mount. G. A., Morris. T. A., Zimmerman. R. H., Barnard. D. R., & Snoddy. E. L. (1990). Management of lone star ticks (Acari: Ixodidae) in recreational areas with acaricide applications, vegetative management, and exclusion of white-tailed deer. *Journal of Medical Entomology, 27*(4), 543–550. https://doi.org/10.1093/jmedent/27.4.543

Blum, L. K., Adamska, J. Z., Martin, D. S., Rebman, A. W., Elliott, S. E., Cao, R., Embers, M. E., Aucott, J. N., Soloski, M. J., & Robinson, W. H. (2018). Robust B cell responses predict rapid resolution of Lyme disease. *Frontiers in Immunology*, *9*, 1634. https://doi.org/10.3389/fimmu.2018.01634

Bobe, J. R., Jutras, B. L., Horn, E. J., Embers, M. E., Bailey, A., Moritz, R. L., Zhang, Y., Soloski, M. J., Ostfeld, R. S., Marconi, R. T., Aucott, J., Ma'ayan, A., Keesing, F., Lewis, K., Ben Mamoun, C., Rebman, A. W., McClune, M. E., Breitschwerdt, E. B., Reddy, P. J., ... & Fallon, B. A. (2021). Recent progress in Lyme disease and remaining challenges. *Frontiers in Medicine*, *8*, 666554. https://doi.org/10.3389/fmed.2021.666554

Bouquet, J., Soloski, M. J., Swei, A., Cheadle, C., Federman, S., Billaud, J. N., Rebman, A. W., Kabre, B., Halpert, R., Boorgula, M., Aucott, J. N., & Chiu, C. Y. (2016). Longitudinal transcriptome analysis reveals a sustained differential gene expression signature in patients treated for acute Lyme disease. *mBio*, *7*(1), e00100–e116. https://doi.org/10.1128/mBio.00100-16

Branda, J. A., Linskey, K., Kim, Y. A., Steere, A. C., & Ferraro, M. J. (2011). Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *53*(6), 541–547. https://doi.org/10.1093/cid/cir464

Bransfield, R. C. (2018). Neuropsychiatric Lyme borreliosis: An overview with a focus on a specialty psychiatrist's clinical practice. *Healthcare, 6*(3), 104. https://doi.org/10.3390/healthcare6030104

Brault, A. C., Savage, H. M., Duggal, N. K., Eisen, R. J., & Staples, J. E. (2018). Heartland virus epidemiology, vector association, and disease potential. *Viruses*, *10*(9), 498. https://doi.org/10.3390/v10090498

Braveman P. (2014). What are health disparities and health equity? We need to be clear. *Public Health Reports, 129*(Suppl 2), 5–8. https://doi.org/10.1177/00333549141291S203

Braveman, P., Arkin, E., Orleans, T., Proctor, D., & Plough, A. (2017). What is health equity? https://www.rwjf.org/en/library/research/2017/05/what-is-health-equity-.html

Briese, T., Kapoor, A., Mishra, N., Jain, K., Kumar, A., Jabado, O. J., & Lipkin, W. I. (2015). Virome capture sequencing enables sensitive viral diagnosis and comprehensive virome analysis. *mBio*, *6*(5), e01491-15. https://doi.org/10.1128/mBio.01491-15

Burlina, P. M., Joshi, N. J., Ng, E., Billings, S. D., Rebman, A. W., & Aucott, J. N. (2019). Automated detection of erythema migrans and other confounding skin lesions via deep learning. *Computers in Biology and Medicine, 105*, 151–156. https://doi.org/10.1016/j.compbiomed.2018.12.007

Butler, A. D., Carlson, M. L., & Nelson, C. A. (2017). Use of a tick-borne disease manual increases accuracy of tick identification among primary care providers in Lyme disease endemic areas. *Ticks and Tick-Borne Diseases*, *8*(2), 262–265. https://doi.org/10.1016/j.ttbdis.2016.11.010

Butzner, M., & Cuffee, Y. (2021). Telehealth interventions and outcomes across rural communities in the United States: Narrative review. *Journal of Medical Internet Research*, *23*(8), e29575. https://doi.org/10.2196/29575

Cadavid, D., Auwaerter, P. G., Rumbaugh, J., & Gelderblom, H. (2016). Antibiotics for the neurological complications of Lyme disease. *Cochrane Database of Systematic Reviews*, *12*, CD006978. https://doi.org/10.1002/14651858.CD006978.pub2

Cameron, D. J., Johnson, L. B., & Maloney, E. L. (2014). Evidence assessments and guideline recommendations in Lyme disease: The clinical management of known tick bites, erythema migrans rashes and persistent disease. *Expert Review of Anti-infective Therapy*, *12*(9), 1103–1135. https://doi.org/10.1586/14787210.2014.940900

Camire, A. C., Hatke, A. L., King, V. L., Millership, J., Ritter, D. M., Sobell, N., Weber, A., & Marconi, R. T. (2021). Comparative analysis of antibody responses to outer surface protein (Osp)A and OspC in dogs vaccinated with Lyme disease vaccines. *The Veterinary Journal*, *273*, 105676. https://doi.org/10.1016/j.tvjl.2021.105676

Carson, A. S., Gardner, A., & Iweala, O. I. (2022). Where's the beef? Understanding allergic responses to red meat in Alpha-gal Syndrome. *Journal of Immunology*, *208*(2), 267–277. https://doi.org/10.4049/jimmunol.2100712

CDC (Centers for Disease Control and Prevention). (2015). Relapsing fever: Distribution. https://www.cdc.gov/relapsing-fever/distribution/index.html

CDC (2020a). Health equity. U.S. Department of Health and Human Services. https://www.cdc.gov/chronicdisease/healthequity/index.htm

CDC. (2020b). Ticks and Lyme disease: Pregnancy and Lyme Disease. https://www.cdc.gov/lyme/resources/toolkit/factsheets/Pregnancy-and-Lyme-Disease-508.pdf

CDC. (2020c). Vector-borne diseases in the United States, 2004-2018. https://www.cdc.gov/ncezid/dvbd/vital-signs/index.html

CDC. (2021a). About social determinants of health (SDOH). https://www.cdc.gov/socialdeterminants/about.html

CDC. (2021b). Broad Agency Announcement (BAA) Number 75D301-22-R-72097. https://sam.gov/opp/056d80ac50ab4205a699dcf794b8ab6a/view

CDC. (2021c). How many people get Lyme disease? https://www.cdc.gov/lyme/stats/humancases.html

CDC. (2021d). Powassan virus: Statistics & maps. https://www.cdc.gov/powassan/statistics.html

CDC. (2021e). Rocky Mountain spotted fever (RMSF): Epidemiology and statistics. https://www.cdc.gov/rmsf/stats/index.html#:~:text=The%20current%20case%20fatality%20rate%20for%20SFRs%20using,lower%20case%20fatality%20rate%20observed%20in%20recent%20decades

CDC. (2021f). Tick removal and testing. https://www.cdc.gov/lyme/removal/

CDC. (2021g). Tickborne disease surveillance data summary. https://www.cdc.gov/ticks/index.html

CDC. (2021h). Ticks: Regions where ticks live. https://www.cdc.gov/ticks/geographic_distribution.html

CDC. (2022a). Lyme disease: Data and surveillance. https://www.cdc.gov/lyme/datasurveillance/index.html

CDC. (2022b). Lyme disease: Lyme carditis. https://www.cdc.gov/lyme/treatment/lymecarditis.html

CDC. (2022c). Powassan virus: Symptoms, diagnosis, and treatment. https://www.cdc.gov/powassan/symptoms.html

CDC. (2022d). Tickborne diseases of the United States: Heartland and Bourbon virus diseases. https://www.cdc.gov/ticks/tickbornediseases/heartland-virus.html

CDC. (2022e). Treatment of Lyme disease. https://www.cdc.gov/lyme/treatment/index.html

CDMRP (Congressionally Directed Medical Research Program). (2022). A 5-year-old gone too soon from untreated Rocky Mountain Spotted Fever. U.S. Department of Defense. https://cdmrp.army.mil/cwg/stories/2019/tony_galbo_profile

Chevinsky, J. R., Tao, G., Lavery, A. M., Kukielka, E. A., Click, E. S., Malec, D., Kompaniyets, L., Bruce, B. B., Yusuf, H., Goodman, A. B., Dixon, M. G., Nakao, J. H., Datta, S. D., MacKenzie, W. R., Kadri, S. S., Saydah, S., Giovanni, J. E., & Gundlapalli, A. V. (2021). Late conditions diagnosed 1-4 months following an initial coronavirus disease 2019 (COVID-19) encounter: A matched-cohort study using inpatient and outpatient administrative data - United States, 1 March-30 June 2020. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 73(Suppl 1), S5–S16. https://doi.org/10.1093/cid/ciab338

Chinuki, Y., Ishiwata, K., Yamaji, K., Takahashi, H., & Morita, E. (2016). Haemaphysalis longicornis tick bites are a possible cause of red meat allergy in Japan. Allergy, 71(3), 421–425. https://doi.org/10.1111/all.12804

Commins, S. P. (2016). Invited commentary: Alpha-gal allergy: Tip of the iceberg to a pivotal immune response. Current Allergy and Asthma Reports, 16(9), 61. https://doi.org/10.1007/s11882-016-0641-6

Commins, S. P. (2020). Diagnosis and management of Alpha-gal Syndrome: Lessons learned from 2,500 patients. *Expert Review of Clinical Immunology, 16*(7), 667–677. https://doi.org/10.1080/174466 6X.2020.1782745

Commins, S. P., James, H. R., Kelly, L. A., Pochan, S. L., Workman, L. J., Perzanowski, M. S., Kocan, K. M., Fahy, J. V., Nganga, L. W., Ronmark, E., Cooper, P. J., & Platts-Mills, T. A. (2011). The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. *The Journal of Allergy and Clinical Immunology*, *127*(5), 1286–1293.e6. https://doi.org/10.1016/j.jaci.2011.02.019

Commins, S. P., James, H. R., Stevens, W., Pochan, S. L., Land, M. H., King, C., Mozzicato, S., & Platts-Mills, T. A. (2014). Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. *Journal of Allergy and Clinical Immunology*, *134*(1), 108–115. https://doi.org/10.1016/j.jaci.2014.01.024

Comstedt, P., Schüler, W., Meinke, A., & Lundberg, U. (2017). The novel Lyme borreliosis vaccine VLA15 shows broad protection against *Borrelia* species expressing six different OspA serotypes. *PLOS ONE*,*12*(9), e0184357. https://doi.org/10.1371/journal.pone.0184357

Conrad, P. A., Kjemtrup, A. M., Carreno, R. A., Thomford, J., Wainwright, K., Eberhard, M., Quick, R., Telford, S. R., 3rd, & Herwaldt, B. L. (2006). Description of *Babesia duncani* n.sp. (Apicomplexa: Babesiidae) from humans and its differentiation from other piroplasms. *International Journal for Parasitology*, *36*(7), 779–789. https://doi.org/10.1016/j.ijpara.2006.03.008

Coughlin, J. M., Yang, T., Rebman, A. W., Bechtold, K. T., Du, Y., Mathews, W. B., Lesniak, W. G., Mihm, E. A., Frey, S. M., Marshall, E. S., Rosenthal, H. B., Reekie, T. A., Kassiou, M., Dannals, R. F., Soloski, M. J., Aucott, J. N., & Pomper, M. G. (2018). Imaging glial activation in patients with post-treatment Lyme disease symptoms: A pilot study using [11C]DPA-713 PET. *Journal of Neuroinflammation*, *15*(1), 346. https://doi.org/10.1186/s12974-018-1381-4

Crispell, G., Commins, S. P., Archer-Hartman, S. A., Choudhary, S., Dharmarajan, G., Azadi, P., & Karim, S. (2019). Discovery of alpha-gal-containing antigens in North American tick species believed to induce red meat allergy. *Frontiers in immunology*, *10*, 1056. https://doi.org/10.3389/fimmu.2019.01056

Crossland, N. A., Alvarez, X., & Embers, M. E. (2018). Late disseminated Lyme disease: Associated pathology and spirochete persistence posttreatment in rhesus macaques. *The American Journal of Pathology*, *188*(3), 672–682. https://doi.org/10.1016/j.ajpath.2017.11.005

Dahlgren, F. S., Holman, R. C., Paddock, C. D., Callinan, L. S., & McQuiston, J. H. (2012). Fatal Rocky Mountain spotted fever in the United States, 1999-2007. *American Journal of Tropical Medicine and Hygiene*, *86*(4), 713–719. https://doi.org/10.4269/ajtmh.2012.11-0453

Dantas-Torres, F. (2015). Climate change, biodiversity, ticks and tick-borne diseases: The butterfly effect. *International Journal for Parasitology: Parasites and Wildlife*, *4*, 452–461. https://doi.org/10.1016/j.ijppaw.2015.07.001

Dattwyler, R. J., Volkman, D. J., Luft, B. J., Halperin, J. J., Thomas, J., & Golightly, M. G. (1988). Seronegative Lyme disease. *The New England Journal of Medicine*, *319*(22), 1441–1446. https://doi.org/10.1056/NEJM198812013192203

Davey, A. (2021). *Presentation by Angel Davey, PhD, to the Access to Care and Education Subcommittee of the 2022 Tick-Borne Disease Working Group.*

Delong, A. K., Blossom, B., Maloney, E. L., & Phillips, S. E. (2012). Antibiotic retreatment of Lyme disease in patients with persistent symptoms: A biostatistical review of randomized, placebo-controlled, clinical trials. *Contemporary Clinical Trials*, *33*(6), 1132–1142. https://doi.org/10.1016/j.cct.2012.08.009

Demma, L. J., Traeger, M. S., Nicholson, W. L., Paddock, C. D., Blau, D. M., Eremeeva, M. E., Dasch, G. A., Levin, M. L., Singleton, J., Jr, Zaki, S. R., Cheek, J. E., Swerdlow, D. L., & McQuiston, J. H. (2005). Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *The New England Journal of Medicine*, *353*(6), 587–594. https://doi.org/10.1056/NEJMoa050043

Dennison, R., Novak, C., Rebman, A., Venkatesan, A., & Aucott, J. (2019). Lyme disease with erythema migrans and seventh nerve palsy in an African-American man. *Cureus*, *11*(12), e6509. https://doi.org/10.7759/cureus.6509

Diuk-Wasser, M. A., Hoen, A. G., Cislo, P., Brinkerhoff, R., Hamer, S. A., Rowland, M., Cortinas, R., Vouch, G., Melton, F., Hickling, G. J., Tsao, J. I., Bunikis, J., Barbour, A. G., Kitron, U., Piesman, J., & Fish, D. (2012). Human risk of infection with *Borrelia burgdorferi,* the Lyme disease agent, in eastern United States. *American Journal of Tropical Medicine and Hygiene, 86*, 320–327. https://doi.org/10.4269/ajtmh.2012.11-0395

Diuk-Wasser, M. A., VanAcker, M. C., & Fernandez, M. P. (2021). Impact of land use changes and habitat fragmentation on the eco-epidemiology of tick-borne diseases. *Journal of Entomology, 58*(4), 1546–1564. https://doi.org/10.1093/jme/tjaa209

Dixon, D. M., Branda, J. A., Clark, S. H., Dumler, J. S., Horowitz, H. W., Perdue, S. S., Pritt, B. S., Sexton, D. J., Storch, G. A., & Walker, D. H. (2021). Ehrlichiosis and Anaplasmosis Subcommittee Report to the Tick-borne Disease Working Group. Ticks and Tick-Borne Diseases, *12*(6), 101823. https://doi.org/10.1016/j.ttbdis.2021.101823

Djulbegovic, B., & Guyatt, G. H. (2017). Progress in evidence-based medicine: A quarter century on. *Lancet*, *390*(10092), 415–423. https://doi.org/10.1016/S0140-6736(16)31592-6

Douglas, T. A., Tamburro, D., Fredolini, C., Espina, B. H., Lepene, B. S., Ilag, L., Espina, V., Petricoin, E. F., 3rd, Liotta, L. A., & Luchini, A. (2011). The use of hydrogel microparticles to sequester and concentrate bacterial antigens in a urine test for Lyme disease. *Biomaterials*, *32*(4), 1157–1166. https://doi.org/10.1016/j.biomaterials.2010.10.004

Dumler, J. S., Madigan, J. E., Pusterla, N., & Bakken, J. S. (2007). Ehrlichioses in humans: Epidemiology, clinical presentation, diagnosis, and treatment. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *45(*Suppl 1), S45–S51. https://doi.org/10.1086/518146

Ebel, G. D. (2010). Update on Powassan virus: Emergence of a North American tick-borne flavivirus. *Annual Review of Entomology, 55*, 95–110. https://doi.org/10.1146/annurev-ento-112408-085446

Eisen, L. (2021). Control of ixodid ticks and prevention of tick-borne diseases in the United States: The prospect of a new Lyme disease vaccine and the continuing problem with tick exposure on residential properties. *Ticks and Tick-borne Diseases, 12*, 101649. https://doi.org/10.1016/j.ttbdis.2021.101649

Eisen, L. (2022). Tick species infesting humans in the United States. *Ticks and Tick-borne Diseases, 13*(6), 102025. https://doi.org/10.1016/j.ttbdis.2022.102025

Eisen, L., & Dolan, M. C. (2016). Evidence for personal protective measures to reduce human contact with blacklegged ticks and for environmentally based control methods to suppress host-seeking black-legged ticks and reduce infection with Lyme disease spirochetes in tick vectors and rodent reservoirs. *Journal of Medical Entomology, 53*, 1063–1092. https://doi.org/10.1093/jme/tjw103

Eisen, L., & Eisen, R. J. (2016). Critical evaluation of the linkage between tick-based risk measures and the occurrence of Lyme disease cases. *Journal of Medical Entomology, 53*, 1050–1062. https://doi.org/10.1093/jme/tjw092

Eisen, L., & Stafford III, K.C. (2021). Barriers to effective tick management and tick-bite prevention in the United States (acari: Ixodidae). *Journal of Medical Entomology, 58*, 1588–1600. https://doi.org/10.1093/jme/tjaa079

Eisen, R. J., Kugeler, K. J., Eisen, L., Beard, C. B., & Paddock, C. D. (2017). Tick-borne zoonoses in the United States: Persistent and emerging threats to human health. *ILAR Journal, 58*(3), 319–335. https://doi.org/10.1093/ilar/ilx005

Eisen, R. J., & Paddock, C. D. (2020). Tick and tickborne pathogen surveillance as a public health tool in the United States. *Journal of Medical Entomology, 58*, 1490–1502. https://doi.org/10.1093/jme/tjaa087

Eisen, R. J., Piesman, J., Zielinski-Gutierrez, E., & Eisen, L. (2012). What do we need to know about Lyme disease ecology to prevent Lyme disease in the northeastern United States? *Journal of Medical Entomology, 49*, 11–22. https://doi.org/10.1603/me11138

Embers, M. E., Barthold, S. W., Borda, J. T., Bowers, L., Doyle, L., Hodzic, E., Jacobs, M. B., Hasenkampf, N. R., Martin, D. S., Narasimhan, S., Phillippi-Falkenstein, K. M., Purcell, J. E., Ratterree, M. S., & Philipp, M. T. (2012). Persistence of *Borrelia burgdorferi* in rhesus macaques following antibiotic treatment of disseminated infection. *PloS One*, *7*(1), e29914. https://doi.org/10.1371/journal.pone.0029914

Embers, M. E., Hasenkampf, N. R., Jacobs, M. B., Tardo, A. C., Doyle-Meyers, L. A., Philipp, M. T., & Hodzic, E. (2017). Variable manifestations, diverse seroreactivity and post-treatment persistence in non-human primates exposed to *Borrelia burgdorferi* by tick feeding. *PloS One*, *12*(12), e0189071. https://doi.org/10.1371/journal.pone.0189071

Eskow, E., Rao, R. V., & Mordechai, E. (2001). Concurrent infection of the central nervous system by *Borrelia burgdorferi* and *Bartonella henselae*: Evidence for a novel tick-borne disease complex. *Archives of Neurology*, *58*(9), 1357–1363. https://doi.org/10.1001/archneur.58.9.1357

Fallon, B. A., Keilp, J. G., Corbera, K. M., Petkova, E., Britton, C. B., Dwyer, E., Slavov, I., Cheng, J., Dobkin, J., Nelson, D. R., & Sackeim, H. A. (2008). A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*, *70*(13), 992–1003. https://doi.org/10.1212/01.WNL.0000284604.61160.2d

Fallon, B. A., Madsen, T., Erlangsen, A., & Benros, M. E. (2021). Lyme Borreliosis and associations with mental disorders and suicidal behavior: A nationwide Danish cohort study. *American Journal of Psychiatry*, *178*(10), 921–931. https://doi.org/10.1176/appi.ajp.2021.20091347

Fallon, B. A., & Nields, J. A. (1994). Lyme disease: A neuropsychiatric illness. *American Journal of Psychiatry, 151*(11), 1571–1583. https://doi.org/10.1176/ajp.151.11.1571

Fallon, B. A., Petkova, E., Keilp, J. G., & Britton, C. B. (2012). A reappraisal of the U.S. clinical trials of post-treatment Lyme disease syndrome. *Open Neurology Journal*, *6*, 79–87. https://doi.org/10.2174/1874205X01206010079

Faruki, H., & Lai-Goldman, M. (2010). Application of a pharmacogenetic test adoption model to six oncology biomarkers. *Personalized Medicine*, *7*(4), 441–450. https://doi.org/10.2217/pme.10.37

Fischhoff, I. R., Bowden, S. E., Keesing, F., & Ostfeld, R. S. (2019). Systematic review and meta-analysis of tick-borne disease risk factors in residential yards, neighborhoods, and beyond. *BMC Infectious Diseases, 19*, 861. https://doi.org/10.1186/s12879-019-4484-3

Fitzgerald, B. L., Graham, B., Delorey, M. J., Pegalajar-Jurado, A., Islam, M. N., Wormser, G. P., Aucott, J. N., Rebman, A. W., Soloski, M. J., Belisle, J. T., & Molins, C. R. (2021). Metabolic response in patients with Post-Treatment Lyme Disease Symptoms/Syndrome. *Clinical Infectious Diseases, 73*(7), e2342–e2349. https://doi.org/10.1093/cid/ciaa1455

Fitzgerald, B. L., Molins, C. R., Islam, M. N., Graham, B., Hove, P. R., Wormser, G. P., Hu, L., Ashton, L. V., & Belisle, J. T. (2020). Host metabolic response in early Lyme disease. *Journal of Proteome Research, 19*(2), 610–623. https://doi.org/10.1021/acs.jproteome.9b00470

Fix, A. D., Pena, C. A., & Strickland, G. T. (2000). Racial differences in reported Lyme disease incidence. *American Journal of Epidemiology*, *152*(8), 756–759. https://doi.org/10.1093/aje/152.8.756

Flaherty, M. G., Kaplan, S. J., & Jerath, M. R. (2017). Diagnosis of life-threatening Alpha-gal food allergy appears to be patient driven. *Journal of Primary Care & Community Health*, *8*(4), 345–348. https://doi.org/10.1177/2150131917705714

Ford, G., Koutsky, T., & Spiwak, L. (2007). A valley of death in the innovation sequence: An economic investigation. *Research Evaluation, 18*. http://dx.doi.org/10.2139/ssrn.1093006

Fukunaga, M., Takahashi, Y., Tsuruta, Y., Matsushita, O., Ralph, D., McClelland, M., & Nakao, M. (1995). Genetic and phenotypic analysis of *Borrelia miyamotoi* sp. nov., isolated from the ixodid tick *Ixodes persulcatus,* the vector for Lyme disease in Japan. *International Journal of Systematic Bacteriology*, *45*(4), 804–810. https://doi.org/10.1099/00207713-45-4-804

Garnett, J. M., Connally, N. P., Stafford III, K. C., & Cartter, M. L. (2011). Evaluation of deer targeted interventions on Lyme disease incidence in Connecticut. *Public Health Reports, 126*(3), 446–454. https://doi.org/10.1177/003335491112600321

Gaudet, E. M., Gould, O. N., & Lloyd, V. (2019). Parenting when children have Lyme disease: Fear, frustration, advocacy. *Healthcare (Basel, Switzerland)*, *7*(3), 95. https://doi.org/10.3390/healthcare7030095

Ginzburg, S. B., Santen, S. A., & Schwartzstein, R. M. (2021). Self-directed learning: A new look at an old concept. *Medical Science Educator*, *31*(1), 229–230. https://doi.org/10.1007/s40670-020-01121-w

Government of Canada. (2022, January 10). Risks of Getting Lyme Disease: Pregnant People. https://www.canada.ca/en/public-health/services/diseases/lyme-disease/prevention-lyme-disease.html#a1

Graf, J. F., Gogolewskim, R., Leach-Bingm, N., Sabatinim, G. A., Molento, M. B., & Bordin, E. L. (2004). Tick control: An industry point of view. *Parasitology, 129*, S427–S442. https://doi.org/10.1017/s0031182004006079

Gu, W., Deng, X., Lee, M., Sucu, Y. D., Arevalo, S., Stryke, D., Federman, S., Gopez, A., Reyes, K., Zorn, K., Sample, H., Yu, G., Ishpuniani, G., Briggs, B., Chow, E. D., Berger, A., Wilson, M. R., Wang, C., Hsu, E., Miller, S., … Chiu, C. Y. (2021). Rapid pathogen detection by metagenomic next-generation sequencing of infected body fluids. *Nature Medicine*, *27*(1), 115–124. https://doi.org/10.1038/s41591-020-1105-z

Gwynne, P. J., Clendenen, L. H., Turk, S. P., Marques, A. R., & Hu, L. T. (2022). Antiphospholipid autoantibodies in Lyme disease arise after scavenging of host phospholipids by *Borrelia burgdorferi*. *Journal of Clinical Investigation, 132*(6). https://doi.org/10.1172/jci152506

Hahn, M. B., Bjork, J. K. H., Neitzel, D. F., Dorr, F. M., Whitemarsh, T., Boegler, K. A., Graham, C. B., Johnson, T. L., Maes, S. E., & Eisen, R. J. (2018). Evaluating acarological risk for exposure to *Ixodes scapularis* and *Ixodes scapularis*-borne pathogens in recreational and residential settings in Washington county, Minnesota. *Ticks and Tick-borne Diseases, 9*, 340–348. https://doi.org/10.1016/j.ttbdis.2017.11.010

Hall, W. J., Chapman, M. V., Lee, K. M., Merino, Y. M., Thomas, T. W., Payne, B. K., Eng, E., Day, S. H., & Coyne-Beasley, T. (2015). Implicit racial/ethnic bias among health care professionals and its influence on health care outcomes: A systematic review. *American Journal of Public Health*, *105*(12), e60–76. https://doi.org/10.2105/AJPH.2015.302903

Hayes, E., & Mead, P. (2004). Lyme disease. *Clinical Evidence, 12*, 1115–1124. https://www.ncbi.nlm.nih.gov/pubmed/15865708

Hein, T. M., Sander, P., Giryes, A., Reinhardt, J. O., Hoegel, J., & Schneider, E. M. (2019). Cytokine expression patterns and single nucleotide polymorphisms (SNPs) in patients with chronic borreliosis. *Antibiotics*, *8*(3), 107. https://doi.org/10.3390/antibiotics8030107

Herc, E., Pritt, B., Huizenga, T., Douce, R., Hysell, M., Newton, D., Sidge, J., Losman, E., Sherbeck, J., & Kaul, D. R. (2018). Probable locally acquired *Babesia divergens*-like infection in woman, Michigan, USA. *Emerging Infectious Diseases*, *24*(8), 1558–1560. https://doi.org/10.3201/eid2408.180309

Herwaldt, B. L., de Bruyn, G., Pieniazek, N. J., Homer, M., Lofy, K. H., Slemenda, S. B., Fritsche, T. R., Persing, D. H., & Limaye, A. P. (2004). *Babesia divergens*-like infection, Washington State. *Emerging Infectious Diseases*, *10*(4), 622–629. https://doi.org/10.3201/eid1004.030377

HHS (U.S. Department of Health and Human Services). (2021). LymeX: Applying Health+ for patient-powered innovations. https://www.hhs.gov/blog/2021/04/12/lymex-applying-health-patient-powered-innovations.html

HHS. (2022). Social Determinants of Health. https://health.gov/healthypeople/priority-areas/social-determinants-health

Hinckley, A. F., Connally, N. P., Meek, J. I., Johnson, B. J., Kemperman, M. M., Feldman, K. A., White, J. L., & Mead, P. S. (2014). Lyme disease testing by large commercial laboratories in the United States. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *59*(5), 676–681. https://doi.org/10.1093/cid/ciu397

Hinckley, A. F., Meek, J. I., Ray, J. A. E., Niesobecki, S. A., Connally, N. P., Feldman, K. A., Jones, E. H., P Backenson, B., White, J. L., Lukacik, G., Kay, A. B., Miranda, W. P., & Mead, P. S. (2016). Effectiveness of residential acaricides to prevent Lyme and other tick-borne diseases in humans. *Journal of Infectious Diseases, 214*, 182–188. https://doi.org/10.1093/infdis/jiv775

Hinckley, A. F., Niesobecki, S. A., Connally, N. P., Hook, S. A., Biggerstaff, B. J., Horiuchi, K. A., Hojgaard, A., Mead, P. S., & Meek, J. I. (2021). Prevention of Lyme and other tickborne diseases using a rodent-targeted approach: A randomized controlled trial in Connecticut. *Zoonoses and Public Health, 68*, 578–587. https://doi.org/10.1111/zph.12844

Hirsch, A. G., Poulsen, M. N., Nordberg, C., Moon, K. A., Rebman, A. W., Aucott, J. N., Heaney, C. D., & Schwartz, B. S. (2020). Risk factors and outcomes of treatment delays in Lyme disease: A population-based retrospective cohort study. *Frontiers in Medicine*, *7*, 560018. https://doi.org/10.3389/fmed.2020.560018

Hodzic, E., Imai, D., Feng, S., & Barthold, S. W. (2014). Resurgence of persisting non-cultivable *Borrelia burgdorferi* following antibiotic treatment in mice. *PloS One*, *9*(1), e86907. https://doi.org/10.1371/journal.pone.0086907

Hook, S. A., Nelson, C. A., & Mead, P. S. (2015). U.S. public's experience with ticks and tick-borne diseases: Results from national HealthStyles surveys. *Ticks and Tick-Borne Diseases*, *6*(4), 483–488. https://doi.org/10.1016/j.ttbdis.2015.03.017

Horn, E. J., Dempsey, G., Schotthoefer, A. M., Prisco, U. L., McArdle, M., Gervasi, S. S., Golightly, M., De Luca, C., Evans, M., Pritt, B. S., Theel, E. S., Iyer, R., Liveris, D., Wang, G., Goldstein, D., & Schwartz, I. (2020). The Lyme Disease Biobank: Characterization of 550 patient and control samples from the East Coast and Upper Midwest of the United States. *Journal of Clinical Microbiology, 58*(6). https://doi.org/10.1128/JCM.00032-20

Hovius, J. W., van Dam, A. P., & Fikrig, E. (2007). Tick-host-pathogen interactions in Lyme borreliosis. *Trends in Parasitology*, *23*(9), 434–438. https://doi.org/10.1016/j.pt.2007.07.001

Huang, L., Yao, Q., Gu, X., Wang, Q., Ren, L., Wang, Y., Hu, P., Liu, M., Xu, J., Zhang, X., Qu, Y., Fan., Y., Li, X., Li, C., Yu, T., Sia, J., Wei, M., Chen, L., Li, Y., … Cao, B. (2021). 1-year outcomes in hospital survivors with COVID-19: A longitudinal cohort study. *The Lancet*, *398*(10302), 747–758. https://doi.org/10.1016/S0140-6736(21)01755-4

Hudson, J., & Khazragui, H. F. (2013). Into the valley of death: Research to innovation. *Drug Discovery Today, 18*, 610–613. https://doi.org/10.1016/j.drudis.2013.01.012

IOM (Institute of Medicine). (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*. National Academies Press. https://doi.org/10.17226/10027

IOM. (2009). *Conflict of Interest in Medical Research, Education, and Practice*. National Academies Press. https://doi.org/10.17226/12598

Jain, K., Tagliafierro, T., Marques, A., Sanchez-Vicente, S., Gokden, A., Fallon, B., Mishra, N., Briese, T., Kapoor, V., Sameroff, S., Guo, C., Marcos, L. A., Hu, L., Lipkin, W. I., & Tokarz, R. (2021). Development of a capture sequencing assay for enhanced detection and genotyping of tick-borne pathogens. *Scientific Reports*, *11*(1), 12384. https://doi.org/10.1038/s41598-021-91956-z

Johnson, L. (2019a). MyLymeData 2019 chart book. https://figshare.com/articles/book/MyLymeData_2019_Chart_Book/8063039/1

Johnson, L. (2019b). MyLymeData stigma and privacy in Lyme disease data: A project of LymeDisease.org. https://figshare.com/articles/poster/MyLymeData_Stigma_and_Privacy_in_Lyme_Disease_Data_A_project_of_LymeDisease_org_2_11_19_xlsx/7704167/1?file=14349281

Johnson, L., Aylward, A., & Stricker, R. B. (2011). Healthcare access and burden of care for patients with Lyme disease: A large United States survey. *Health Policy*, *102*(1), 64–71. https://doi.org/10.1016/j.healthpol.2011.05.007

Johnson, L. B., & Maloney, E. L. (2022). Access to care in Lyme disease: Clinician barriers to providing care. *Healthcare, 10,* 1882. https://doi.org/10.3390/healthcare10101882

Johnson, L., Shapiro, M., & Mankoff, J. (2018). Removing the mask of average treatment effects in chronic Lyme disease research using big data and subgroup analysis. *Healthcare (Basel)*, *6*(4). https://doi.org/10.3390/healthcare6040124

Johnson, L., Shapiro, M., Stricker, R. B., Vendrow, J., Haddock, J., & Needell, D. (2020). Antibiotic treatment response in chronic Lyme disease: Why do some patients improve while others do not? *Healthcare (Basel)*, *8*(4). https://doi.org/10.3390/healthcare8040383

Johnson, L., Wilcox, S., Mankoff, J., & Stricker, R. B. (2014). Severity of chronic Lyme disease compared to other chronic conditions: A quality of life survey. *PeerJ*, *2*, e322. https://doi.org/10.7717/peerj.322

Johnson, L. B., & Smalley, J. B. (2019). Engaging the patient: Patient-centered research. In K. L. Hall, A. L. Vogel, & R. T. Croyle (Eds.), *Strategies for Team Science Success: Handbook of Evidence-Based Principles for Cross-Disciplinary Science and Practical Lessons Learned From Health Researchers* (pp. 135–147). Springer International Publishing. https://doi.org/10.1007/978-3-030-20992-6_10

Jongejan, F., & Uilenberg, G. (2004). The global importance of ticks. *Parasitology, 129 Suppl*, S3–S14. https://doi.org/10.1017/s0031182004005967

Joung, H. A., Ballard, Z. S., Wu, J., Tseng, D. K., Teshome, H., Zhang, L., Horn, E. J., Arnaboldi, P. M., Dattwyler, R. J., Garner, O. B., Di Carlo, D., & Ozcan, A. (2020). Point-of-care serodiagnostic test for early-stage Lyme disease using a multiplexed paper-based immunoassay and machine learning. *ACS Nano*, *14*(1), 229–240. https://doi.org/10.1021/acsnano.9b08151

Keesing, F., Mowry, S., Bremer, W., Duerr, S., Evans, A., Fischhoff, I., Hinckley, A., Hook, S., Keating, F., Pendleton, J., Pfister, A., Teator, M., & Ostfeld, R. (2022). Effects of tick-control interventions on tick abundance, human encounters with ticks, and incidence of tickborne diseases in residential neighborhoods, New York, USA. *Emerging Infectious Disease, 28*, 957. https://doi.org/10.3201/eid2805.211146

Keesing, F., & Ostfeld, R. S. (2018). The tick project: Testing environmental methods of preventing tick-borne diseases. *Trends in Parasitology, 34*, 447–450. https://doi.org/10.1016/j.pt.2018.02.008

Kehoe, E. R., Fitzgerald, B. L., Graham, B., Islam, M. N., Sharma, K., Wormser, G. P., Belisle, J. T., & Kirby, M. J. (2022). Biomarker selection and a prospective metabolite-based machine learning diagnostic for Lyme disease. *Scientific Reports*, *12*(1), 1478. https://doi.org/10.1038/s41598-022-05451-0

Kennedy, A. C., & Marshall, E. (2021). Lone star ticks (*Amblyomma americanum*): An emerging threat in Delaware. *Delaware Journal of Public Health*, *7*(1), 66–71. https://doi.org/10.32481/djph.2021.01.013

Khoury, J. K., Khoury, N. C., Schaefer, D., Chitnis, A., & Hassen, G. W. (2018). A tick-acquired red meat allergy. *The American Journal of Emergency Medicine*, *36*(2), 341.e1–341.e3. https://doi.org/10.1016/j.ajem.2017.10.044

Kilpatrick, A. M., Dobson, A. D. M., Levi, T., Salkeld D. J., Swei, A., Ginsberg, H. S., Kjemtrup, A., Padgett, K. A., Jensen, P. M., Fish, D., Ogden, N. H., & Diuk-Wasser, M. A. (2017). Lyme disease ecology in a changing world: Consensus, uncertainty and critical gaps for improving control. *Philosophical Transactions of the Royal Society B: Biological Sciences, 372*. https://doi.org/10.1098/rstb.2016.0117

Kilpatrick, H. J., LaBonte, A. M., & Stafford III, K. C. (2014). The relationship between deer density, tick abundance, and human cases of Lyme disease in a residential community. *Journal of Medical Entomology, 51*(4), 777–784. https://doi.org/10.1603/me13232

King, J. L., Smith, A. D., Mitchell, E. A., & Allen, M. S. (2017). Validation of droplet digital PCR for the detection and absolute quantification of *Borrelia* DNA in *Ixodes scapularis* ticks. *Parasitology*, *144*(4), 359–367. https://doi.org/10.1017/S0031182016001864

Kirsch, D. (2019, September 12). Exploring FDA approval pathways for medical devices. MassDevice. https://www.massdevice.com/exploring-fda-approval-pathways-for-medical-devices/

Klempner, M. S., Baker, P. J., Shapiro, E. D., Marques, A., Dattwyler, R. J., Halperin, J. J., & Wormser, G. P. (2013). Treatment trials for post-Lyme disease symptoms revisited. *American Journal of Medicine*, *126*(8), 665–669. https://doi.org/10.1016/j.amjmed.2013.02.014

Klempner, M. S., Hu, L. T., Evans, J., Schmid, C. H., Johnson, G. M., Trevino, R. P., Norton, D., Levy, L., Wall, D., McCall, J., Kosinski, M., & Weinstein, A. (2001). Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *The New England Journal of Medicine*, *345*(2), 85–92. https://doi.org/10.1056/NEJM200107123450202

Kohler, J. (1990). Lyme borreliosis in neurology and psychiatry. *Fortschritte der Medizin, 108*(10), 191–193, 197. https://europepmc.org/article/med/2187778

Kopsco, H. L., Duhaime, R. J., & Mather, T. N. (2021). Assessing public tick identification ability and tick bite riskiness using passive photograph-based crowdsourced tick surveillance. *Journal of Medical Entomology*, *58*(2), 837–846. https://doi.org/10.1093/jme/tjaa196

Kosoy, O. I., Lambert, A. J., Hawkinson, D. J., Pastula, D. M., Goldsmith, C. S., Hunt, D. C., & Staples, J. E. (2015). Novel thogotovirus associated with febrile illness and death, United States, 2014. *Emerging Infectious Diseases*, *21*(5), 760–764. https://doi.org/10.3201/eid2105.150150

Krause, P. J. (2019). Human babesiosis. *International Journal for Parasitology*, *49*(2), 165–174. https://doi.org/10.1016/j.ijpara.2018.11.007

Krause, P. J., Auwaerter, P. G., Bannuru, R. R., Branda, J. A., Falck-Ytter, Y. T., Lantos, P. M., Lavergne, V., Meissner, H. C., Osani, M. C., Rips, J. G., Sood, S. K., Vannier, E., Vaysbrot, E. E., & Wormser, G. P. (2021). Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA): 2020 Guideline on Diagnosis and Management of Babesiosis. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 72*(2), 185–189. https://doi.org/10.1093/cid/ciab050

Krause, P. J., Hendrickson, J. E., Steeves, T. K., & Fish, D. (2015). Blood transfusion transmission of the tick-borne relapsing fever spirochete *Borrelia miyamotoi* in mice. *Transfusion*, *55*(3), 593–597. https://doi.org/10.1111/trf.12879

Krause, P. J., Lepore, T., Sikand, V. K., Gadbaw, J., Burke, G., Telford, S. R., Brassard, P., Pearl, D., Azlanzadeh, J., Christianson, D., McGrath, D., & Spielman, A. (2000). Atovaquone and azithromycin for the treatment of babesiosis. *New England Journal of Medicine*, *343*(20), 1454–1458. https://academic.oup.com/cid/article/72/1/e1/6010652

Krupp, L. B., Hyman, L. G., Grimson, R., Coyle, P. K., Melville, P., Ahnn, S., Dattwyler, R., & Chandler, B. (2003). Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*, *60*(12), 1923–1930. https://doi.org/10.1212/01.wnl.0000071227.23769.9e

Kugeler, K. J., Jordan, R. A., Schulze, T. L., Griffith, K. S., & Mead, P. S. (2015). Will culling white-tailed deer prevent Lyme disease? *Zoonoses and Public Health*, *63*(5), 337–345. https://doi.org/10.1111/zph.12245

Kugeler, K. J., Schwartz, A. M., Delorey, M. J., Mead, P. S., & Hinckley, A. F. (2021). Estimating the frequency of Lyme disease diagnoses, United States, 2010-2018. *Emerging Infectious Diseases*, *27*(2), 616–619. https://doi.org/10.3201/eid2702.202731

Kumar, A., O'Bryan, J., & Krause, P. J. (2021). The global emergence of human babesiosis. *Pathogens*, *10*(11), 1447. https://doi.org/10.3390/pathogens10111447

Lai-Goldman, M., & Faruki, H. (2008). Abacavir hypersensitivity: A model system for pharmacogenetic test adoption. *Genetics in Medicine, 10*(12), 874–878. https://doi.org/10.1097/GIM.0b013e31818de71c

Lantos, P. M., Rumbaugh, J., Bockenstedt, L. K., Falck-Ytter, Y. T., Aguero-Rosenfeld, M. E., Auwaerter, P. G., Baldwin, K., Bannuru, R. R., Belani, K. K., Bowie, W. R., Branda, J. A., Clifford, D. B., DiMario, F. J., Halperin, J. J., Krause, P. J., Lavergne, V., Liang, M. H., Meissner, H. C., Nigrovic, L. E., Nocton, J. J. J., Osani, M. C., ... & Zemel, L. S. (2021). Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. *Clinical Infectious Diseases*, *72*(1), e1–e48. https://doi.org/10.1093/cid/ciaa1215

Largent, E. A., Weissman, J. S., Gupta, A., Abraham, M., Rozenblum, R., Lynch, H. F., & Cohen, I. G. (2018). Patient-centered outcomes research: Stakeholder perspectives and ethical and regulatory oversight issues. *IRB*, *40*(1), 7–17.

Levin, M., Apostolovic, D., Biedermann, T., Commins, S. P., Iweala, O. I., Platts-Mills, T. A. E., Savi, E., van Hage, M., & Wilson, J. M. (2019). Galactose -1,3-galactose phenotypes: Lessons from various patient populations. *Annals of Allergy, Asthma, & Immunol*, *122*(6), 598–602. https://doi.org/10.1016/j.anai.2019.03.021

Liburd, L. C., Hall, J. E., Mpofu, J. J., Williams, S. M., Bouye, K., & Penman-Aguilar, A. (2020). Addressing health equity in public health practice: Frameworks, promising strategies, and measurement considerations. *Annual Review of Public Health*, *41*, 417–432. https://doi.org/10.1146/annurev-publhealth-040119-094119

Liebell, D. (2020). Effect of Soliman Auricular Allergy Treatment (SAAT) on IgE-mediated reactions due to exposure to mammalian meat oligosaccharide, galactose- -1,3-galactose. *American Journal of Biomedical and Life Sciences, 8*, 189. https://doi.org/10.11648/j.ajbls.20200805.18

Logigian, E. L., Kaplan, R. F., & Steere, A. C. (1999). Successful treatment of Lyme encephalopathy with intravenous ceftriaxone. *Journal of Infectious Disease*, *180*(2), 377–383. https://doi.org/10.1086/314860

Lyon, J., & Seung, H. (2019). Genetic variation in the ABCB1 gene associated with post-treatment Lyme disease syndrome status. *Meta Gene, 21*, 100589. https://doi.org/10.1016/j.mgene.2019.100589

Mac, S., da Silva, S. R., & Sander, B. (2019). The economic burden of Lyme disease and the cost-effectiveness of Lyme disease interventions: A scoping review. *PLoS ONE, 14*(1), e0210280. https://doi.org/10.1371/journal.pone.0210280

Maccallini, P., Bonin, S., & Trevisan, G. (2018). Autoimmunity against a glycolytic enzyme as a possible cause for persistent symptoms in Lyme disease. *Medical Hypotheses*, *110*, 1–8. https://doi.org/10.1016/j.mehy.2017.10.024

Mader, E. M., Ganser, C., Geiger, A., Harrington, L. C., Foley, J., Smith, R. L., Mateus-Pinilla, N., Teel, P. D., & Eisen, R. J. (2021). A survey of tick surveillance and control practices in the United States. *Journal of Medical Entomology, 58*(4), 1503–1512. https://doi.org/10.1093/jme/tjaa094

Madison-Antenucci, S., Kramer, L. D., Gebhardt, L. L., & Kauffman, E. (2020). Emerging tick-borne diseases. *Clinical Microbiology Reviews, 33*(2), e00083-18. https://doi.org/10.1128/CMR.00083-18

Magni, R., Luchini, A., Liotta, L., & Molestina, R. E. (2020). Proteomic analysis reveals pathogen-derived biomarkers of acute babesiosis in erythrocytes, plasma, and urine of infected hamsters. *Parasitology Research, 119*(7), 2227–2235. https://doi.org/10.1007/s00436-020-06712-5

Maggi, R., Breitschwerdt, E. B., Qurollo, B., & Miller, J. C. (2021). Development of a multiplex droplet digital PCR assay for the detection of *Babesia, Bartonella*, and *Borrelia* species. *Pathogens, 10*(11), 1462. https://doi.org/10.3390/pathogens10111462

Maggi, R. G., Mozayeni, B. R., Pultorak, E. L., Hegarty, B. C., Bradley, J. M., Correa, M., & Breitschwerdt, E. B. (2012). *Bartonella* spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region. *Emerging Infectious Diseases, 18*(5), 783–791. https://doi.org/10.3201/eid1805.111366

Magni, R., Espina, B. H., Shah, K., Lepene, B., Mayuga, C., Douglas, T. A., Espina, V., Rucker, S., Dunlap, R., Petricoin, E. F., Kilavos, M. F., Poretz, D. M., Irwin, G. R., Shor, S. M., Liotta, L. A., & Luchini, A. (2015). Application of nanotrap technology for high sensitivity measurement of urinary outer surface protein A carboxyl-terminus domain in early stage Lyme borreliosis. *Journal of Translational Medicine, 13*, 346. https://doi.org/10.1186/s12967-015-0701-z

Maggi, R. G., Richardson, T., Breitschwerdt, E. B., & Miller, J. C. (2020). Development and validation of a droplet digital PCR assay for the detection and quantification of *Bartonella* species within human clinical samples. *Journal of Microbiological Methods, 176*, 106022. https://doi.org/10.1016/j.mimet.2020.106022

Maraspin, V., Lusa, L., Blejec, T., Ruzic-Sabljic, E., Pohar Perme, M., & Strle, F. (2020). Course and outcome of erythema migrans in pregnant women. *Journal of Clinical Medicine, 9*(8). https://doi.org/10.3390/jcm9082364

Marx, G. E., Leikauskas, J., Lindstrom, K., Mann, E., Reagan-Steiner, S., Matkovic, E., Read, J. S., Kelso, P., Kwit, N. A., Hinckley, A. F., Levine, M. A., & Brown, C. (2020). Fatal Lyme carditis in New England: Two case reports. *Annals of Internal Medicine, 172*(3), 222–224. https://doi.org/10.7326/L19-0483

Massarotti, E. M., Luger, S. W., Rahn, D. W., Messner, R. P., Wong, J. B., Johnson, R. C., & Steere, A. C. (1992). Treatment of early Lyme disease. *The American Journal of Medicine, 92*(4), 396–403. https://doi.org/10.1016/0002-9343(92)90270-l

Mathisson, D. C., Kross, S. M., M Palmer, I., & Diuk-Wasser, M. A. (2021). Effect of vegetation on the abundance of tick vectors in the northeastern United States: A review of the literature. *Journal of Medical Entomology, 58*, 2030–2037. https://doi.org/10.1093/jme/tjab098

Matias, J., Kurokawa, C., Sajid, A., Narasimhan, S., Arora, G., Diktas, H., Lynn, G. E., DePonte, K., Pardi, N., Valenzuela, J. G., Weissman, D., & Fikrig, E. (2021). Tick immunity using mRNA, DNA and protein-based Salp14 delivery strategies. *Vaccine, 39*(52), 7661–7668. https://doi.org/10.1016/j.vaccine.2021.11.003

Mead, P., Hook, S., Niesobecki, S., Ray, J., Meek, J., Delorey, M., Prue, C., & Hinckley, A. (2018). Risk factors for tick exposure in suburban settings in the northeastern United States. *Ticks and Tick-borne Diseases, 9*, 319–324. https://doi.org/10.1016/j.ttbdis.2017.11.006

Mead, P., Petersen, J., & Hinckley, A. (2019). Updated CDC recommendation for serologic diagnosis of Lyme disease. *Morbidity and Mortality Weekly Report, 68*(32), 703. https://doi.org/10.15585/mmwr.mm6832a4

Molaei, G., Eisen, L. M., Price, K. J., & Eisen, R. J. (2022). Range expansion of native and invasive ticks: A looming public health threat. *The Journal of Infectious Diseases*, *226*(3), 370–373. https://doi.org/10.1093/infdis/jiac249

Molins, C. R., Ashton, L. V., Wormser, G. P., Andre, B. G., Hess, A. M., Delorey, M. J., Pilgard, M. A., Johnson, B. J., Webb, K., Islam, M. N., Pegalajar-Jurado, A., Molla, I., Jewett, M. W., & Belisle, J. T. (2017). Metabolic differentiation of early Lyme disease from southern tick-associated rash illness (STARI). *Science Translational Medicine, 9*(403). https://doi.org/10.1126/scitranslmed.aal2717

Molins, C. R., Ashton, L. V., Wormser, G. P., Hess, A. M., Delorey, M. J., Mahapatra, S., Schriefer, M. E., & Belisle, J. T. (2015). Development of a metabolic biosignature for detection of early Lyme disease. *Clinical Infectious Diseases, 60*(12), 1767–1775. https://doi.org/10.1093/cid/civ185

Molins, C. R., Sexton, C., Young, J. W., Ashton, L. V., Pappert, R., Beard, C. B., & Schriefer, M. E. (2014). Collection and characterization of samples for establishment of a serum repository for Lyme disease diagnostic test development and evaluation. *Journal of Clinical Microbiology*, *52*(10), 3755–3762. https://doi.org/10.1128/JCM.01409-14

Monath, T. P. (2013). Vaccines against diseases transmitted from animals to humans: A one health paradigm. *Vaccine, 31*, 5321–5338. https://doi.org/10.1016/j.vaccine.2013.09.029

National Institutes of Health. (2008, July). *Lyme Disease, The Facts, The Challenge.* NIH Publication No. 08-7045.

Ndawula, C. (2021). From bench to field: A guide to formulating and evaluating anti-tick vaccines delving beyond efficacy to effectiveness. *Vaccines, 9*, 1185. https://doi.org/10.3390/vaccines9101185

Nelson, C. A., Saha, S., Kugeler, K. J., Delorey, M. J., Shankar, M. B., Hinckley, A. F., & Mead, P. S. (2015). Incidence of clinician-diagnosed Lyme disease, United States, 2005-2010. *Emerging Infectious Diseases*, *21*(9), 1625–1631. https://doi.org/10.3201/eid2109.150417

Nelson, C. A., Starr, J. A., Kugeler, K. J., & Mead, P. S. (2016). Lyme disease in Hispanics, United States, 2000-2013. *Emerging Infectious Diseases*, *22*(3), 522–525. https://doi.org/10.3201/eid2203.151273

NIHCE (National Institute for Health and Care Excellence). (2018). Lyme disease: Evidence. https://www.nice.org.uk/guidance/ng95/evidence

Nofchissey, R. A., Deardorff, E. R., Blevins, T. M., Anishchenko, M., Bosco-Lauth, A., Berl, E., Lubelczyk, C., Mutebi, J. P., Brault, A. C., Ebel, G. D., & Magnarelli, L. A. (2013). Seroprevalence of Powassan virus in New England deer, 1979-2010. *American Journal of Tropical Medicine and Hygiene*, *88*(6), 1159–1162. https://doi.org/10.4269/ajtmh.12-0586

Nowakowski, J., Nadelman, R. B., Sell, R., McKenna, D., Cavaliere, L. F., Holmgren, D., Gaidici, A., & Wormser, G. P. (2003). Long-term follow-up of patients with culture-confirmed Lyme disease. *The American Journal of Medicine*, *115*(2), 91–96. https://doi.org/10.1016/s0002-9343(03)00308-5

Nuss, A., Sharma, A., & Gulia-Nuss, M. (2021). Genetic manipulation of ticks: A paradigm shift in tick and tick-borne disease research. *Frontiers in Cell and Infection Microbiology, 11*, 678037. https://doi.org/10.3389/fcimb.2021.678037

Nyblade, L., Stockton, M. A., Giger, K., Bond, V., Ekstrand, M. L., Lean, R. M., Mitchell, E. M. H., Nelson, R.E., Sapag, J. C., Siraprapasiri, T., Turan, J., & Wouters, E. (2019). Stigma in health facilities: Why it matters and how we can change it. *BMC Medicine*, *17*(1), 25. https://doi.org/10.1186/s12916-019-1256-2

O'Bier, N. S., Hatke, A. L., Camire, A. C., & Marconi, R. T. (2021). Human and veterinary vaccines for Lyme disease. *Current Issues in Molecular Biology*, *42*, 191–222. https://doi.org/10.21775/cimb.042.191

O'Brien Pott, M., Blanshan, A. S., Huneke, K. M., Baasch Thomas, B. L., & Cook, D. A. (2021a). Barriers to identifying and obtaining CME: A national survey of physicians, nurse practitioners and physician assistants. *BMC Medical Education*, *21*(1), 168. https://doi.org/10.1186/s12909-021-02595-x

O'Brien Pott, M., Blanshan, A. S., Huneke, K. M., Baasch Thomas, B. L., & Cook, D. A. (2021b). What influences choice of continuing medical education modalities and providers? A national survey of U.S. physicians, nurse practitioners, and physician assistants. *Academic Medicine*, *96*(1), 93–100. https://doi.org/10.1097/ACM.0000000000003758

Office of Disease Prevention and Health Promotion. (n.d.). Social determinants of health. U.S. Department of Health and Human Services. https://health.gov/healthypeople/objectives-and-data/social-determinants-health

OIDP (Office of Infectious Diseases and HIV/AIDS Policy). (2022). *The 2022 National Inventory of Tick-Borne Diseases and Associated Illnesses.* U.S. Department of Health and Human Services. [insert link when available]

Pachner, A. R. (1988). *Borrelia burgdorferi* in the nervous system: The new "great imitator." *Annals of the New York Academy of Sciences, 539*(1), 56–64. https://doi.org/10.1111/j.1749-6632.1988.tb31838.x

Pattanaik, D., Lieberman, P., Lieberman, J., Pongdee, T., & Keene, A. T. (2018). The changing face of anaphylaxis in adults and adolescents. *Annals of Allergy, Asthma, & Immunology*, *121*(5), 594–597. https://doi.org/10.1016/j.anai.2018.07.017

Paules, C. I., Marston, H. D., Bloom, M. E., & Fauci, A. S. (2018). Tickborne diseases – confronting a growing threat. *New England Journal of Medicine, 379*, 701–703. https://doi.org/10.1056/NEJMp1807870

Pegalajar-Jurado, A., Fitzgerald, B. L., Islam, M. N., Belisle, J. T., Wormser, G. P., Waller, K. S., Ashton, L. V., Webb, K. J., Delorey, M. J., Clark, R. J., & Molins, C. R. (2018). Identification of urine metabolites as biomarkers of early Lyme disease. *Scientific Reports, 8*(1), 12204. https://doi.org/10.1038/s41598-018-29713-y

Perea, A. E., Hinckley, A. F., & Mead, P. S. (2020). Evaluating the potential misuse of the Lyme disease surveillance case definition. *Public Health Reports*, *135*(1), 16–17. https://doi.org/10.1177/0033354919890024

Pennsylvania Department of Environmental Protection. (2022). Asian Longhorned Tick. https://www.dep.pa.gov/Business/ProgramIntegration/Vector-Management/Ticks/Pages/Asian-Longhorned-Tick.aspx

Petzke, M. M., Volyanskyy, K., Mao, Y., Arevalo, B., Zohn, R., Quituisaca, J., Wormser, G. P., Dimitrova, N., & Schwartz, I. (2020). Global transcriptome analysis identifies a diagnostic signature for early disseminated Lyme disease and its resolution. *mBio, 11*(2), e00047-20. https://doi.org/10.1128/mBio.00047-20

Pew. (2021). The role of lab-developed tests in the in vitro diagnostics market. https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market

Piacentino, J. D., & Schwartz, B. S. (2002). Occupational risk of Lyme disease: An epidemiological review. *Occupational and Environmental Medicine*, *59*, 75–84. https://doi.org/10.1136/oem.59.2.75

Piesman, J., & Eisen, L. (2008). Prevention of tick-borne diseases. *Annual Review of Entomology, 53*, 323–343. https://doi.org/10.1146/annurev.ento.53.103106.093429

Platonov, A. E., Karan, L. S., Kolyasnikova, N. M., Makhneva, N. A., Toporkova, M. G., Maleev, V. V., Fish, D., & Krause, P. J. (2011). Humans infected with relapsing fever spirochete *Borrelia miyamotoi*, Russia. *Emerging Infectious Diseases*, *17*(10), 1816–1823. https://doi.org/10.3201/eid1710.101474

Platt, J. L., & Merritt, T. H. (2022). Exploratory survey research study of 2,000 Alpha-gal Syndrome patients: Symptoms and experiences in the United States. *Journal of Allergy and Clinical Immunology*, *149*(2), Supplement, AB322. https://doi.org/10.1016/j.jaci.2021.12.030

Platts-Mills, T. A. E., Schuyler, A. J., Commins, S. P., Merritt, T. K., McGintee, E. E., James, H., Workman, L. J., & Wilson, J. M. (2018). Characterizing the geographic distribution of the Alpha-gal Syndrome: Relevance to lone star ticks (*Amblyomma americanum*) and Rickettsia. *Journal of Allergy and Clinical Immunology*, *141*(2), Supplement, AB147. https://doi.org/10.1016/j.jaci.2017.12.470

Podsiadły, E., Chmielewski, T., & Tylewska-Wierzbanowska, S. (2003). *Bartonella henselae* and *Borrelia burgdorferi* infections of the central nervous system. *Annals of the New York Academy of Sciences*, *990*, 404–406. https://doi.org/10.1111/j.1749-6632.2003.tb07400.x

Pöyhönen, H., Nurmi, M., Peltola, V., Alaluusua, S., Ruuskanen, O., & Lähdesmäki, T. (2017). Dental staining after doxycycline use in children. *The Journal of Antimicrobial Chemotherapy*, *72*(10), 2887–2890. https://doi.org/10.1093/jac/dkx245

Pritt B. S. (2021). Unbiased metagenomics–a new tool for detecting early Lyme disease? *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *73*(7), e2362–e2363. https://doi.org/10.1093/cid/ciaa854

Purdue, S. (2021). *Presentation by Sam Purdue, PhD, to the Access to Care and Education Subcommittee of the 2022 Tick-Borne Disease Working Group*.

Radtke, F. A., Ramadoss, N., Garro, A., Bennett, J. E., Levas, M. N., Robinson, W. H., Nigrovic, P. A., Nigrovic, L. E., & for Pedi Lyme Net. (2021). Serologic response to *Borrelia* antigens varies with clinical phenotype in children and young adults with Lyme disease. *Journal of Clinical Microbiology*, *59*(11), e0134421. https://doi.org/10.1128/JCM.01344-21

Rebman, A. W., Bechtold, K. T., Yang, T., Mihm, E. A., Soloski, M. J., Novak, C. B., & Aucott, J. N. (2017). The clinical, symptom, and quality-of-life characterization of a well-defined group of patients with posttreatment Lyme disease syndrome. *Frontiers in Medicine*, *4*, 224. https://doi.org/10.3389/fmed.2017.00224

Rebman, A. W., Crowder, L. A., Kirkpatrick, A., & Aucott, J. N. (2015). Characteristics of seroconversion and implications for diagnosis of post-treatment Lyme disease syndrome: Acute and convalescent serology among a prospective cohort of early Lyme disease patients. *Clinical Rheumatology*, *34*(3), 585–589. https://doi.org/10.1007/s10067-014-2706-z

Rebman, A. W., Soloski, M. J., & Aucott, J. N. (2015). Sex and gender impact Lyme disease immunopathology, diagnosis and treatment. In: Klein, S., & Roberts, C. (eds.). *Sex and Gender Differences in Infection and Treatments for Infectious Diseases*. Springer, Cham. https://doi.org/10.1007/978-3-319-16438-0_12

Rebman, A. W., Yang, T., Mihm, E. A., Novak, C. B., Yoon, I., Powell, D., Geller, S. A., & Aucott, J. N. (2021). The presenting characteristics of erythema migrans vary by age, sex, duration, and body location. *Infection*, *49*(4), 685–692. https://doi.org/10.1007/s15010-021-01590-0

Rego, R. O. M., Trentelman, J. J. A., Anguita, J., Nijhof, A. M., Sprong, H., Klempa, B., Hajdusek, O., Tomás-Cortázar, J., Azagi, T., Strnad, M., Knorr, S., Sima, R., Jalovecka, M., Fumačová Havlíková, S., Ličková, M., Sláviková, M., Kopacek, P., Grubhoffer, L., & Hovius, J. W. (2019). Counterattacking the tick bite: Towards a rational design of anti-tick vaccines targeting pathogen transmission. *Parasites & Vectors*, *12*(1), 229. https://doi.org/10.1186/s13071-019-3468-x

Richer, L. M., Brisson, D., Melo, R., Ostfeld, R. S., Zeidner, N., & Gomes-Solecki, M. (2014). Reservoir targeted vaccine against *borrelia burgdorferi*: A new strategy to prevent Lyme disease transmission. *Journal of Infectious Diseases, 209*, 1972–1980. https://doi.org/10.1093/infdis/jiu005

Rosenberg, R., Lindsey, N. P., Fischer, M., Gregory, C. J., Hinckley, A. F., Mead, P. S., Paz-Bailey, G., Waterman, S. H., Drexler, N. A., Kersh, G. J., Hooks, H., Partridge, S. K., Visser, S. N., Beard, C. B., & Petersen, L. R. (2018). Vital signs: Trends in reported vectorborne disease cases – United States and territories, 2004-2016. *Morbidity and Mortality Weekly Report, 67*(17), 496–501. https://doi.org/10.15585/mmwr.mm6717e1

Roy, A. (2021). Examining mosquito and tick surveillance and control capacity at the local level. *Journal of Public Health Management and Practice*, *27*(6), 618–620. https://doi.org/10.1097/PHH.0000000000001435

Rutschman, A. S. (2021, October 5). How Theranos' faulty blood tests got to market – and what that shows about gaps in FDA regulation. The Conversation. https://theconversation.com/how-theranos-faulty-blood-tests-got-to-market-and-what-that-shows-about-gaps-in-fda-regulation-168050

Sajid, A., Matias, J., Arora, G., Kurokawa, C., DePonte, K., Tang, X., Lynn, G., Wu, M.-J., Pal, U., Strank Norma, O., Pardi, N., Narasimhan, S., Weissman, D., & Fikrig, E. (2021). mRNA vaccination induces tick resistance and prevents transmission of the Lyme disease agent. *Science Translational Medicine*, *13*(620), eabj9827. https://doi.org/10.1126/scitranslmed.abj9827

Savage, H. M., Godsey, M. S., Jr., Panella, N. A., Burkhalter, K. L., Manford, J., Trevino-Garrison, I. C., Straily, A., Wilson, S., Bowen, J., & Raghavan, R. K. (2018). Surveillance for tick-borne viruses near the location of a fatal human case of Bourbon virus (Family Orthomyxoviridae: Genus Thogotovirus) in Eastern Kansas, 2015. *Journal of Medical Entomology*, *55*(3), 701–705. https://doi.org/10.1093/jme/tjx251

Schiller, Z. A., Rudolph, M. J., Toomey, J. R., Ejemel, M., LaRochelle, A., Davis, S. A., Lambert, H. S., Kern, A., Tardo, A. C., Souders, C. A., Peterson, E., Cannon, R. D., Ganesa, C., Fazio, F., Mantis, N. J., Cavacini, L. A., Sullivan-Bolyai, J., Hu, L. T., Embers, M. E., . . . Wang, Y. (2021). Blocking *Borrelia burgdorferi* transmission from infected ticks to nonhuman primates with a human monoclonal antibody. *The Journal of Clinical Investigation*, *131*(11). https://doi.org/10.1172/JCI144843

Schwartz, B. S., & Goldstein, M. D. (1989). Lyme disease: A review for the occupational physician. *Journal of Occupational Medicine, 31*, 735–742. https://doi.org/10.1097/00043764-198909000-00010

Schwartz, B. S., Goldstein, M. D., & Childs, J. E. (1994). Longitudinal study of *Borrelia burgdorferi* infection in new jersey outdoor workers, 1988-1991. *American Journal of Epidemiology, 139*, 504–512. https://doi.org/10.1093/oxfordjournals.aje.a117033

Shirts, B. H. (2020, April 15). STAT. We'll see more shortages of diagnostic tests if the FDA has its way. https://www.statnews.com/2020/04/15/diagnostic-tests-shortages-fda-decision/

Smith, C., Halse, T. A., Shea, J., Modestil, H., Fowler, R. C., Musser, K. A., Escuyer, V., & Lapierre, P. (2020). Assessing nanopore sequencing for clinical diagnostics: A comparison of next-generation sequencing (NGS) methods for *Mycobacterium tuberculosis*. *Journal of Clinical Microbiology*, *59*(1), e00583-20. https://doi.org/10.1128/JCM.00583-20

Solar, O., & Irwin, A. (2010). A conceptual framework for action on the social determinants of health: Social determinants of health discussion paper 2. World Health Organization. https://www.who.int/publications/i/item/9789241500852

Soliman, M. (2014). Perception of stress and coping strategies by medical students at King Saud University, Riyadh, Saudi Arabia. *Journal of Taibah University Medical Sciences, 9*(1), 30–35. https://doi.org/10.1016/j.jtumed.2013.09.006

Soloski, M. J., Crowder, L. A., Lahey, L. J., Wagner, C. A., Robinson, W. H., & Aucott, J. N. (2014). Serum inflammatory mediators as markers of human Lyme disease activity. *PloS One*, *9*(4), e93243. https://doi.org/10.1371/journal.pone.0093243

Sonenshine, D. (2018). Range expansion of tick disease vectors in North America: Implications for spread of tick-borne disease. *International Journal of Environmental Research and Public Health, 15*, 478. https://doi.org/10.3390/ijerph15030478

Springer, Y. P., & Johnson, P. T. J. (2018). Large-scale health disparities associated with Lyme disease and human monocytic ehrlichiosis in the United States, 2007-2013. *PLoS One*, *13*(9), e0204609. https://doi.org/10.1371/journal.pone.0204609

Stafford III, K. C., & Williams, S. C. (2017). Deer-targeted methods: A review of the use of topical acaricides for the control of ticks on white-tailed deer. *Journal of Integrated Pest Management, 8*(1), 19. https://doi.org/10.1093/jipm/pmx014

Stafford III, K. C., Williams, S. C., & Molaei, G. (2017). Integrated pest management in controlling ticks and tick-associated diseases. *Journal of Integrated Pest Management*, *8*(1). https://doi.org/10.1093/jipm/pmx018

Stafford III, K. C., Williams, S. C., Oosterwijk, J. G. V., Linske, M. A., Zatechka, S., Richer, L. M., Molaei, G., Przybyszewski, C., & Wikel, S. K. (2020). Field evaluation of a novel oral reservoir-targeted vaccine against *Borrelia burgdorferi* utilizing an inactivated whole-cell bacterial antigen expression vehicle. *Experimental and Applied Acarology, 20*, 257–268. https://doi.org/10.1007/s10493-019-00458-1

Steere, A. C., & Angelis, S. M. (2006). Therapy for Lyme arthritis: Strategies for the treatment of antibiotic-refractory arthritis. *Arthritis & Rheumatology*, *54*(10), 3079–3086. https://doi.org/10.1002/art.22131

Steere, A. C., Levin, R. E., Molloy, P. J., Kalish, R. A., Abraham, J. H., 3rd, Liu, N. Y., & Schmid, C. H. (1994). Treatment of Lyme arthritis. *Arthritis & Rheumatology*, *37*(6), 878–888. https://doi.org/10.1002/art.1780370616

Steere, A. C., McHugh, G., Damle, N., & Sikand, V. K. (2008). Prospective study of serologic tests for Lyme disease. *Clinical Infectious Diseases*, *47*(2), 188–195. https://doi.org/10.1086/589242

Strle, K., Shin, J. J., Glickstein, L. J., & Steere, A. C. (2012). Association of a toll-like receptor 1 polymorphism with heightened Th1 inflammatory responses and antibiotic-refractory Lyme arthritis. *Arthritis and Rheumatism*, *64*(5), 1497–1507. https://doi.org/10.1002/art.34383

Strle, F., Wormser, G. P., Mead, P., Dhaduvai, K., Longo, M. V., Adenikinju, O., Soman, S., Tefera, Y., Maraspin, V., Lotric-Furlan, S., Ogrinc, K., Cimperman, J., Ruzic-Sabljic, E., & Stupica, D. (2013). Gender disparity between cutaneous and non-cutaneous manifestations of Lyme borreliosis. *PLoS One*, *8*(5), e64110. https://doi.org/10.1371/journal.pone.0064110

Sudre, C. H., Murray, B., Varsavsky, T., Graham, M. S., Penfold, R. S., Bowyer, R. C., Pujol, J. C., Klaser, K., Antonelli, M., Canas, L. S., Molteni, E., Modat, M., Jorge Cardoso, M., May, A., Ganesh, S., Davies, R., Nguyen, L. H., Drew, D. A., Astley, C. M., Joshi, A. D., … Steves, C. J. (2021). Attributes and predictors of long COVID. *Nature Medicine, 27*(4), 626–631. https://doi.org/10.1038/s41591-021-01292-y

Telford, S. R., 3rd, & Wormser, G. P. (2010). *Bartonella* spp. transmission by ticks not established. *Emerging Infectious Diseases*, *16*(3), 379–384. https://doi.org/10.3201/eid1603.090443

Testing.com. (2021a). Commercial laboratory tests and FDA approval. https://www.testing.com/articles/commercial-tests-fda-approval/

Testing.com. (2021b). Laboratory-developed Tests (LDTs). https://www.testing.com/articles/laboratory-developed-tests/

Tetens, M. M., Haahr, R., Dessau, R. B., Krogfelt, K. A., Bodilsen, J., Andersen, N. S., Møller, J. K., Roed, C., Christiansen, C. B., Ellermann-Eriksen, S., Bangsborg, J. M., Hansen, K., Andersen, C. O., Lebech, A. M., Obel, N., & Omland, L. H. (2021). Assessment of the risk of psychiatric disorders, use of psychiatric hospitals, and receipt of psychiatric medication among patients with Lyme neuroborreliosis in Denmark. *JAMA Psychiatry, 78*(2), 177–186. https://doi.org/10.1001/JAMAPSYCHIATRY.2020.2915

Tick-Borne Disease Working Group. (2018). *2018 Report to Congress*. U.S. Department of Health and Human Services. https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf

Tick-Borne Disease Working Group. (2020). *2020 Report to Congress*. U.S. Department of Health and Human Services. https://www.hhs.gov/sites/default/files/tbdwg-2020-report_to-ongress-final.pdf

Tracy, K. E., & Baumgarth, N. (2017). *Borrelia burgdorferi* manipulates innate and adaptive immunity to establish persistence in rodent reservoir hosts. *Frontiers in Immunology, 8,* 116. https://doi.org/10.3389/fimmu.2017.00116

Training, Education, Access to Care, and Reimbursement Subcommittee. (2020). *Report to the Tick-Borne Disease Working Group*. U.S. Department of Health and Human Services. https://www.hhs.gov/ash/advisory-committees/tickbornedisease/reports/training-education-access-to-care-and-reimbursement-subcomm-2020/index.html

Tran, N. K., Albahra, S., May, L., Waldman, S., Crabtree, S., Bainbridge, S., & Rashidi, H. (2021). Evolving applications of artificial intelligence and machine learning in infectious diseases testing. *Clinical Chemistry, 68*(1), 125–133. https://doi.org/10.1093/clinchem/hvab239

Tsao, J. I., Hamer, S. A., Han, S., Sidge, J. L., & Hickling, G. J. (2021). The contribution of wildlife hosts to the rise of ticks and tick-borne diseases in North America. *Journal of Medical Entomology, 58*(4), 1565–1587. https://doi.org/10.1093/jme/tjab047

Turk, S. P., Lumbard, K., Liepshutz, K., Williams, C., Hu, L., Dardick, K., Wormser, G. P., Norville, J., Scavarda, C., McKenna, D., Follmann, D., & Marques, A. (2019). Post-treatment Lyme disease symptoms score: Developing a new tool for research. *PLOS ONE*, *14*(11), e0225012. https://doi.org/10.1371/journal.pone.0225012

Van Nunen, S. A., O'Connor, K. S., Clarke, L. R., Boyle, R. X., & Fernando, S. L. (2009). An association between tick bite reactions and red meat allergy in humans. *Medical Journal of Australia*, *190*(9), 510–511. https://doi.org/10.5694/j.1326-5377.2009.tb02533.x

Vannier, E. G., Diuk-Wasser, M. A., Ben Mamoun, C., & Krause, P. J. (2015). Babesiosis. *Infectious Disease Clinics of North America*, *29*(2), 357–370. https://doi.org/10.1016/j.idc.2015.02.008

Vannier, E., & Krause, P. J. (2009). Update on babesiosis. *Interdisciplinary Perspectives on Infectious Diseases*, *2009*, 984568–984568. https://doi.org/10.1155/2009/984568

Vannier, E., & Krause, P. J. (2012). Human babesiosis. *The New England Journal of Medicine*, *366*(25), 2397–2407. https://doi.org/10.1056/NEJMra1202018

van Oosterwijk, J. G., & Wikel, S. K. (2021). Resistance to ticks and the path to anti-tick and transmission blocking vaccines. *Vaccines, 9*, 725. https://doi.org/10.3390/vaccines9070725

Waddell, L. A., Greig, J., Lindsay, L. R., Hinckley, A. F., & Ogden, N. H. (2018). A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn. *PLoS One*, *13*(11), e0207067. https://doi.org/10.1371/journal.pone.0207067

Wang, Y., Kern, A., Boatright, N. K., Schiller, Z. A., Sadowski, A., Ejemel, M., Souders, C. A., Reimann, K. A., Hu, L., Thomas, W. D., Jr., & Klempner, M. S. (2016). Pre-exposure prophylaxis with OspA-specific human monoclonal antibodies protects mice against tick transmission of Lyme disease spirochetes. *The Journal of Infectious Diseases*, *214*(2), 205–211. https://doi.org/10.1093/infdis/jiw151

Wanga, V., Chevinsky, J. R., Dimitrov, L. V., Gerdes, M. E., Whitfield, G. P., Bonacci, R. A., Nji, M., Hernandez-Romieu, A. C., Rogers-Brown, J. S., McLeod, T., Rushmore, J., Lutfy, C., Bushman, D., Koumans, E., Saydah, S., Goodman, A. B., Coleman King, S. M., Jackson, B. R., & Cope, J. R. (2021). Long-term symptoms among adults tested for SARS-CoV-2 - United States, January 2020-April 2021. *MMWR. Morbidity and Mortality Weekly Report, 70*(36), 1235–1241. https://doi.org/10.15585/mmwr.mm7036a1

Way, H., Williams, G., Hausman-Cohen, S., & Reeder, J. (2021). Genomics as a clinical decision support tool: Successful proof of concept for improved and outcomes. *Journal of Personalized Medicine*, *11*(7), 596. https://doi.org/10.3390/jpm11070596

White, A., & Gaff, H. (2018). Review: Application of tick control technologies for blacklegged, lone star, and American dog ticks. *Journal of Integrated Pest Management, 9*, 12, 1–12. https://doi.org/10.1093/jipm/pmy006

The White House. (2021). Exec. Order No. 13985. https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/

Wikel, S. K. (2018). Ticks and tick-borne infections: Complex ecology, agents, and host interactions. *Veterinary Science, 5*, 60. https://doi.org/10.3390/vetsci5020060

Wikel, S. K. (2022). Changing geographic ranges of human biting ticks and implications for tick-borne zoonoses in North America. *Zoonotic Diseases*, *2*(3), 126–146. https://doi.org/10.3390/zoonoticdis2030013

Williams, S. C., Little, E. A. H., Stafford III, K. C., Molaei, G., & Linske, M. A. (2018). Integrated control of juvenile *Ixodes scapularis* parasitizing *Peromyscus leucopus* in residential settings in Connecticut, United States. *Ticks and Tick-borne Diseases, 9*, 1310–1316. https://doi.org/10.1016/j.ttbdis.2018.05.014

Wilson, M., Glaser, K. C., Adams-Fish, D., Boley, M., Mayda, M., & Molestina, R. E. (2015). Development of droplet digital PCR for the detection of *Babesia microti* and *Babesia duncani*. *Experimental Parasitology*, *149*, 24–31. https://doi.org/10.1016/j.exppara.2014.12.003

Wong L. (2008). Data analysis in qualitative research: a brief guide to using NVivo. *Malaysian Family Physician: The Official Journal of the Academy of Family Physicians of Malaysia*, *3*(1), 14–20.

Wormser, G. P., Dattwyler, R. J., Shapiro, E. D., Halperin, J. J., Steere, A. C., Klempner, M. S., Krause, P. J., Bakken, J. S., Strle, F., Stanek, G., Bockenstedt, L., Fish, D., Dumler, J. S., & Nadelman, R. B. (2006). The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 43*(9), 1089–1134. https://doi.org/10.1086/508667

Yong, S. J. (2021). Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. *Infectious Diseases*, *53*(10), 737–754. https://doi.org/10.1080/23744235.2021.1924397

Zhang, X., Meltzer, M. I., Pena, C. A., Hopkins, A., B., L. Wroth, & Fixt, A. D. (2006). Economic impact of Lyme disease. *Emerging Infectious Diseases, 12*, 653–660. https://doi.org/10.3201/eid1204.050602