

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



The 2022 Tick-Borne Disease National Inventory was prepared by Rose Li and Associates, Inc. (RLA), under contract to the Office of the Assistant Secretary of Health (OASH) [Contract No. 47QRAA19D00D7].

The inventory objective is to provide the Tick-Borne Disease Working Group with an assessment of published and unpublished research, and efforts within federal agencies, states, and private organizations from January 1, 2018, to June 30, 2022 regarding tick-borne diseases and associated illnesses. The report provides an overview of the national response to tick-borne diseases and identifies areas of greatest need. RLA associates who authored this document include Christina Deuschle, Zahra Ehtesham, Cecelia Garcia, Cat Thomson, Meghan Walsh, and Joseph Waring.

The views expressed in this document do not necessarily reflect those of the Tick-Borne Disease Working Group or the sponsoring agency.

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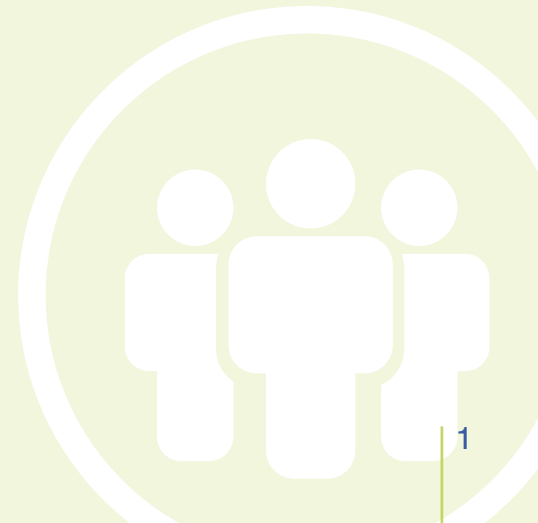
Executive Summary

The 2022 Tick-Borne Disease National Inventory is the most comprehensive tick-borne disease data collection effort to date. This report captures basic, clinical, and translational research conducted from 2018 to mid-2022 in areas of prevention, treatment, surveillance, diagnosis, and duration of illness in individuals with tick-borne diseases and associated illnesses. The literature review is augmented with survey results characterizing tick-borne disease funding, programs, and related activities across participating federal agencies, states, and private organizations. This multipronged approach captures current trends in tick-borne disease research and organizational support and identifies critical gaps in understudied and underserved areas.

The thorough multi-year scoping review of tick-borne diseases showed a year-over-year increase in all research, with projected publications in 2022 expected to exceed those of 2021. Most publications were case reports or surveys, with fewer experimental or observational studies. Broadly, diagnosis and disease surveillance were the principal areas of focus in both the published and unpublished literature, while pathogenesis, clinical presentation, and disease treatment were underrepresented. Tick-borne disease research largely focused on Lyme disease, with fewer publications examining diseases such as southern tick-associated rash illness, Bourbon virus, relapsing fever, and Alpha-gal Syndrome, among others. Analyses of grey literature captured novel and emerging research across the research spectrum, including encouraging progress in surveillance and vaccine technologies, as well as in public awareness and educational interventions.

Findings revealed significant gaps 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.

The literature review complemented the survey component, which captured current federal agency, state, and private efforts to mitigate tick-borne diseases and associated illnesses. Results indicated that the amount of federal funding and initiatives increased from 2018 to 2021. Federal agencies currently support a wide range of epidemiologic, research, preventative, and capacity building and technical assistance activities, as well as the development of diagnostic and treatment protocols for tick-borne diseases. In 2019, the National Institutes of Health published a Strategic Plan for Tickborne Disease Research, and the U.S. Department of Health and Human Services launched LymeX Innovation Accelerator, a public-private partnership with the Steven & Alexandra Cohen Foundation. In 2020, the Centers for Disease Control and



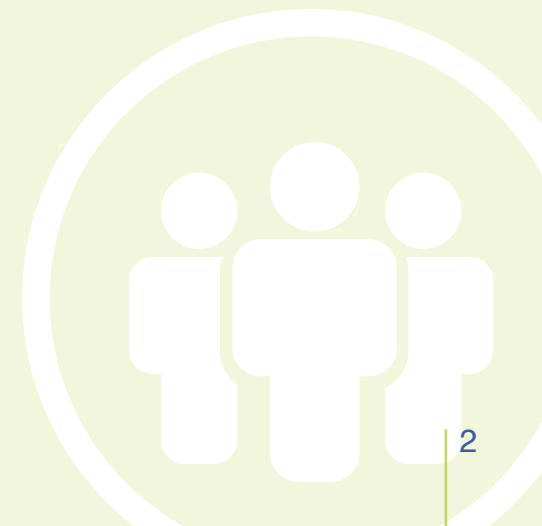
Prevention (CDC) initiated its National Tick Surveillance Program to develop the National Public Health Framework for the Prevention and Control of Vector-Borne Diseases in Humans. CDC has also published continuing education modules for providers and educational materials for both providers and the public.

Private organizations, working independently and in concert with agencies, also drive initiatives to close the gaps in research, diagnostics, access to care, and prevention of tick-borne diseases and associated illnesses. With some attention to health equity, private funders have placed particular focus on engaging the public—through education, advocacy, and citizen science—and enabling research with trial recruitment and data collection using extensive patient surveys. Future plans include the establishment of new and unique partnerships to further advance these initiatives and promote innovative technologies.

Although findings reveal increasing attention at the federal level and within the private sphere, significant discrepancies among states relating to tick-borne diseases remain. Because of small state participation numbers, survey results alone provide an incomplete picture of state-level tick-borne disease response; however, supplemented by additional sources, findings suggest significant disparities among states regarding education, surveillance, and prevention. Future development of quantifiable tools to measure state performance would better identify these gaps and encourage progress across time and between states and regions.

Despite significant investment at all levels to respond to tick-borne diseases and associated illnesses, the combined response remains inadequate. In addition to health equity, several other overarching gaps became apparent in the National Inventory analysis. Prevention products and diagnostic technologies are badly needed, yet there is no clear path to bring them to market, and little has been done to remove existing barriers. Also of great need, a national biorepository of well-characterized human samples reflective of all stages of illness would propel research forward, particularly that which would help chronically ill patients or those with less common tick-borne diseases and associated illnesses. However, this resource is not yet developed.

Broadly, the gaps identified in this report leave segments of the public undereducated about the risks of tick encounters and underserved when the need for care arises. Interdisciplinary approaches are essential in tackling this complex public health issue. Furthermore, representative research and coordinated, long-term, equitable efforts are key to successful prevention, surveillance, diagnosis, treatment, and care across all regions in the country. Expanding research, increasing state initiatives, and continuing agency and organizational support is vital for maintaining progress against tick-borne diseases and associated illnesses.



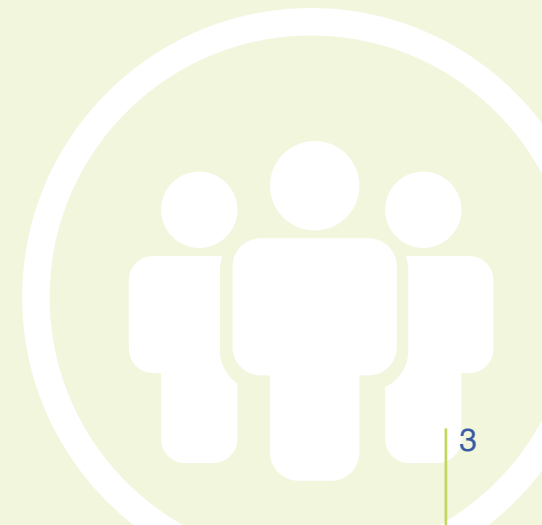
Chapter 1: Introduction

Tick-borne diseases and associated illnesses are a serious and growing public health problem in the United States. They represent greater than 75% of all reported infections transmitted by ticks, mites, and insects, including mosquitos (Eisen & Eisen 2018; Rosenberg et al., 2018). Lyme disease is the most reported tick-borne disease. The Centers for Disease Control and Prevention (CDC) estimate that more than 476,000 new cases of Lyme disease are diagnosed each year (Kugeler et al., 2021a).

CDC recognizes that nine tick species are responsible for transmitting at least 18 disease-causing bacteria, viruses, and parasites in the United States (CDC, 2018). Nearly half of these were discovered during just the past two decades (Eisen & Paddock, 2021), and researchers continue to identify new and emerging diseases and conditions associated with tick bites. One such condition is Alpha-gal Syndrome (AGS), a potentially life-threatening allergy to foods, products, and medications containing ingredients derived from mammals. AGS is associated with the lone star tick (*Amblyomma americanum*), which historically occurred in several southeastern and southern states but is expanding into the Northeast and Midwest (Monzón et al., 2016). In addition to inducing an allergic response, the lone star tick can transmit six disease-causing pathogens, including the bacteria responsible for Rocky Mountain spotted fever (RMSF) (CDC, 2018). Similarly, bites from other tick species infected with more than one pathogen can cause people to develop multiple simultaneous illnesses, compounding the existing challenges of diagnosis and treatment and increasing the risk of long-term illness.

New tick-borne disease cases have been increasing in recent years, and tick species are expanding their geographic ranges, putting more people in more states at potential risk. In fact, ticks that transmit human disease are found in all contiguous United States and Alaska (Rosenberg et al., 2018), and human activities combined with a changing climate only favor the presence of ticks near people (Alkishe et al., 2021; Bouchard et al., 2019; Dantas-Torres, 2015; Sonenshine, 2018). Although these statistics characterize the expansiveness of the problem, it is vitally important to establish a clear accounting of how the United States is responding to the complex issues involving ticks and the illnesses associated with them.

The Tick-Borne Disease National Inventory was designed to provide a comprehensive overview of the national response to tick-borne diseases as a public health issue in the United States. It reports on a cross-section of collected data from multiple sources to inform its objective. For example, the inventory begins with a rapid scoping review to assess the compilation of tick-borne disease research. This comprehensive review captures all published and unpublished literature produced in the United States between January 1, 2018, and June 30, 2022. The review is followed by the survey component, which



was conducted to characterize devoted tick-borne disease funding and related activities across federal agencies, states, and private organizations in areas of research, programs, and public health initiatives since 2018. Additional state data, for example from annual published reports, are included to supplement the state survey material.

The Tick-Borne Disease National Inventory is the most comprehensive tick-borne disease data collection effort to date, with the goals to provide clearer insight into the current national response to tick-borne diseases and to uncover the areas of greatest need. The information contained herein can help direct efforts to underserved and understudied areas within the national tick-borne disease landscape, maximize future investments by informing policy and funding decisions, and provide a tested evaluation for subsequent tick-borne disease data collection efforts.

Background

The Tick-Borne Disease National Inventory was commissioned by the Tick-Borne Disease Working Group (hereafter referred to as the “Working Group”), a federal advisory committee established by the 2016 21st Century Cures Act. The group’s mission is to provide a biannual report that reviews

- ongoing tick-borne disease research related to causes, prevention, treatment, surveillance, diagnosis, diagnostics, duration of illness, and intervention for individuals with tick-borne-diseases;
- advances made pursuant to such research; and
- federal activities related to tick-borne diseases.

The Working Group is housed at the Office of the Assistant Secretary for Health (OASH) in the U.S. Department of Health and Human Services and is supported by staff of the Office of Infectious Disease and HIV/AIDS Policy (OIDP). To achieve its mission, the Working Group provides subject matter expertise, identifies priorities, reviews the federal response, helps ensure interagency coordination and minimize overlap, identifies gaps, and provides recommendations to improve these efforts.

Two prior cycles of the Working Group published Reports to Congress in 2018 and 2020. For each of these reports, the Working Group conducted small-scale inventories of federal activities and research related to tick-borne diseases (Table 1). The inventory results are synthesized, including needs assessments, in the Working Group’s reports.

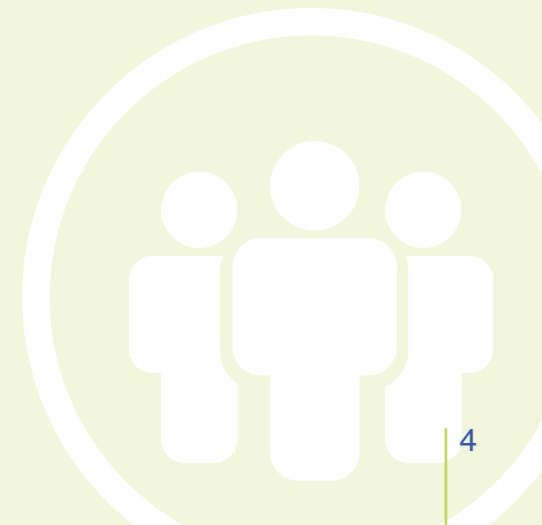


Table 1. Tick-Borne Disease Working Group Federal Inventories, 2018 and 2020

Year	2018	2020
Agencies Surveyed	National Institutes of Health U.S. Department of Defense U.S. Department of Health and Human Services	Centers for Disease Control and Prevention Centers for Medicare & Medicaid Services* National Institutes of Health U.S. Department of Agriculture U.S. Department of Defense U.S. Department of Veterans Affairs U.S. Food and Drug Administration
Data Captured	Lyme Disease or other tick-borne diseases: <ul style="list-style-type: none"> • Projects for fiscal years (FY) 2010–2018 • Publications for FY2010–FY2017 	Lyme disease or other tick-borne diseases: <ul style="list-style-type: none"> • Projects and publications for FY2017–FY2019 Medicarefee-for-service utilization and payments associated with Lyme disease for FY2016
Location of Survey Synthesis	Tick-Borne Disease Working Group 2018 Report to Congress , Appendix D. Federal Inventory, pp. 90-92	Tick-Borne Disease Working Group 2020 Report to Congress , Chapter 9: Federal Inventory, pp. 93-97

*Because the 2020 Federal Inventory questionnaire was not specifically tailored to the Centers for Medicare & Medicaid Services, responses were minimal.

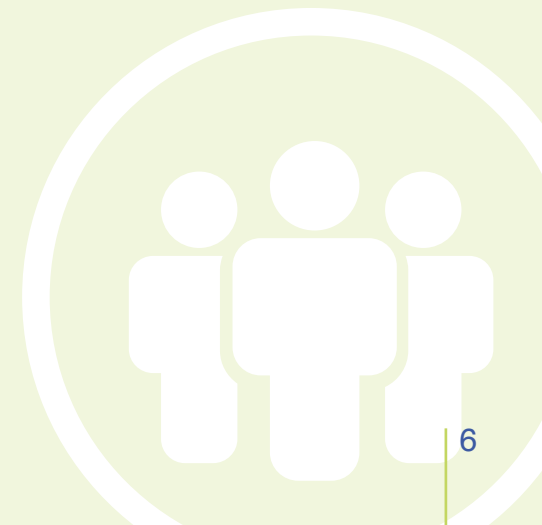
The Working Group's 2020 cycle also included the preparation of three topic development briefs to gain a preliminary understanding of available evidence about unresolved issues including increases in tick-borne diseases in the United States, diagnostic tests for tick-borne diseases, and persistent symptoms of Lyme disease. A complete description of the topic development briefs and their findings can be found on the [Working Group's website](#).

Rationale and Objectives

To build on the work of the 2018 and 2020 Working Groups and complement the third Report to Congress (2022), the Tick-Borne Disease National Inventory represents a comprehensive data collection on tick-borne disease research and public health activities. The inventory's purpose is to quantify research and surveillance of tick-borne diseases and associated illnesses in the United States, including

- activities related to causes, prevention, treatment, surveillance, diagnosis, diagnostics, duration of illness, and intervention for individuals with tick-borne diseases; and
- basic, clinical, and translational research pertaining to pathogenesis, prevention diagnosis, and treatment of tick-borne diseases.

This effort is intended to aid the Working Group in further identifying advances, overlaps, and gaps in tick-borne disease research and activities.



Chapter 2: Methods

With more funding available than in previous years, the 2022 Working Group was able to expand the breadth and depth of previous federal inventory efforts to include additional survey components and an exhaustive literature review.

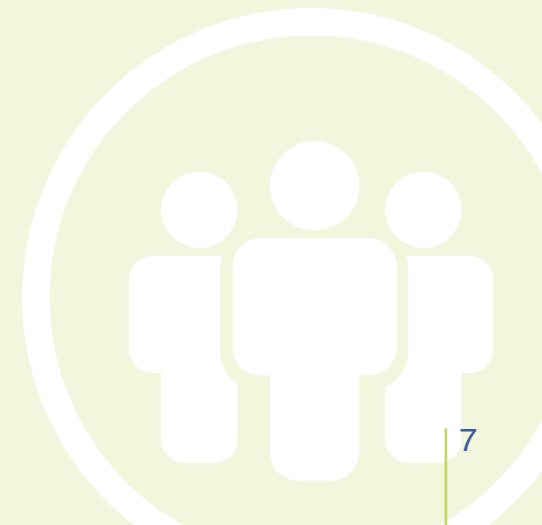
The complete Tick-Borne Disease National Inventory consists of the following data collection methods:

- A rapid scoping review of published and unpublished literature from January 1, 2018 to June 30, 2022
- A survey of five federal agencies, five states, and seven private organizations

The inventory began with a rapid scoping review of literature with the goal of generating an independent assessment of the research environment associated with tick-borne diseases and associated illnesses. Based on Arksey and O'Malley's scoping review framework (2005), the review captured unpublished and published literature reflecting basic, clinical, and translational research related to human tick-borne diseases, conducted in the United States, and dated January 1, 2018, to June 30, 2022.

Using previous federal inventory questionnaires as a basis, survey tools were developed and tailored specifically for federal agencies, states, and private funding organizations. The questions solicited general information about funding and devoted staffing levels for tick-borne disease research and activities and specific information about investments that align with the Working Group's subcommittee priorities. Five federal agencies, five states, and seven private funding organizations participated with rates of 71%, 56%, and 86%, respectively. To complement the state survey, state data were collected from CDC, state reports, and other available sources where relevant.

The remainder of this document reports the results of both the scoping review and the survey. Detailed methods and limitations are provided in the corresponding chapters.



Chapter 3: Scoping Review of Literature

Introduction

A scoping review of literature was conducted to gain a comprehensive perspective of tick-borne diseases and associated illnesses research. The review was designed to provide an independent assessment of the research environment and to identify gaps, advances, and overlaps, particularly in priority areas identified by the 2022 Working Group and its subcommittees. Composed of both published and unpublished literature, the review was designed to complement the surveys of federal agencies, state and local entities, and private organizations, as part of this larger federal inventory report.

Methods

The scoping review is an overview of the current landscape of literature concerning human tick-borne diseases and associated illnesses in the United States between January 1, 2018, and June 30, 2022. The design was based on Arksey and O'Malley's framework (2005), which was further refined by Daudt et al. (2013), and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

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. The review aimed to scope existing published and unpublished literature to examine the extent, range, and nature of research activities, identify research gaps and overlaps, and summarize and disseminate research findings.

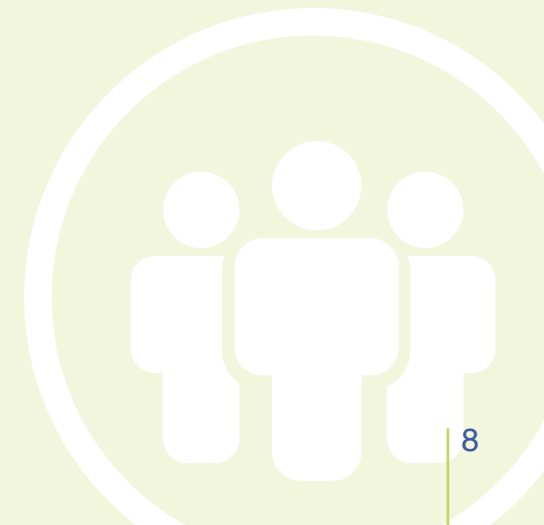
Inclusion and Exclusion Criteria

Summarized in Table 2, the inclusion and exclusion criteria were developed to meet the parameters previously set for the scoping review. The list of tick-borne diseases and associated illnesses included AGS, anaplasmosis, babesiosis, bartonellosis (as a coinfection), *Borrelia mayonii*, *Borrelia miyamotoi*, Bourbon virus, Colorado tick fever, ehrlichiosis, filariasis, Heartland virus, Lyme disease, Powassan disease, Q Fever, *Rickettsia parker* rickettsiosis, RMSF, Southern tick-associated rash illness (STARI), tick-borne relapsing fever, tularemia, and typhus fever rickettsiosis.

To meet the inclusion criteria, all studies had to report on the etiology, prevention, treatment, surveillance, diagnosis, diagnostics, and/or duration of illness of tick-borne diseases and associated illnesses in humans in the United States. Also included were studies reporting on tick surveillance, prevalence of

Scoping Review Research Question

What is the state of current research regarding tick-borne diseases and related illnesses across the research continuum that includes basic, clinical, and translational research in the United States since 2018?

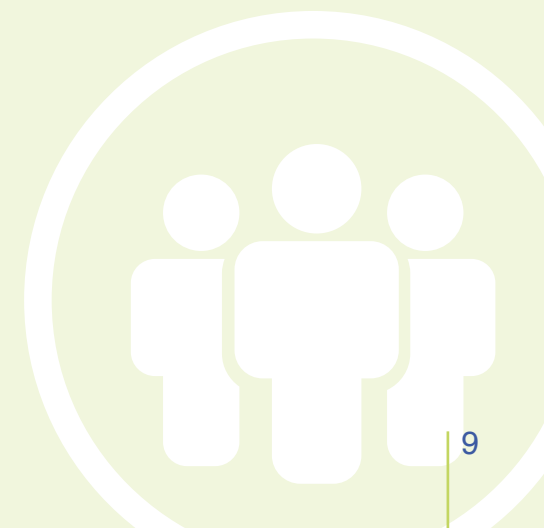


disease among humans, and tick control methods. The unpublished literature search included dissertations and theses, preprints, conference proceedings, and registered clinical trials with data reported also from January 1, 2018, to June 30, 2022.

Literature was excluded if it reported on animal models, tick biology, or tick-borne diseases and associated illnesses outside the United States. Editorials, comments, viewpoints, and research program budgets were also excluded. The unpublished literature search excluded terminated, suspended, or withdrawn clinical trials. Additional state reports published from January 1, 2018, to June 30, 2022, supplemented the state survey information in Chapter 4 where appropriate.

Table 2. Scoping Review of Literature: Inclusion and Exclusion Criteria

Inclusion Criteria
Any research article published from January 1, 2018, to June 30, 2022, that discusses research pertaining to tick-borne diseases and associated illnesses (see list below) in the United States in humans
Any article that describes information related to etiology, prevention, treatment, surveillance, diagnosis, diagnostics, and duration of illness for individuals with tick-borne diseases and associated illnesses
Any research article that describes tick surveillance
Any research article that describes information related to tick-borne diseases and associated illnesses during blood transfusions, blood donations, and organ transplants
Published: Case studies, case reports, guidelines, and systematic reviews
Unpublished: Dissertations and theses, preprints, conference proceedings, and registered clinical trials with data reported from January 1, 2018, to June 30, 2022
Available in the English language
Exclusion Criteria
Any research article that discusses research pertaining to tick-borne diseases and associated illnesses outside the United States
Editorials, reviews, comments, replies, correspondences, viewpoints, and protocols
Research articles related to flea-borne diseases only
Research articles related to tick-borne diseases and associated illnesses in animals
Unpublished: Terminated, suspended, or withdrawn clinical trials



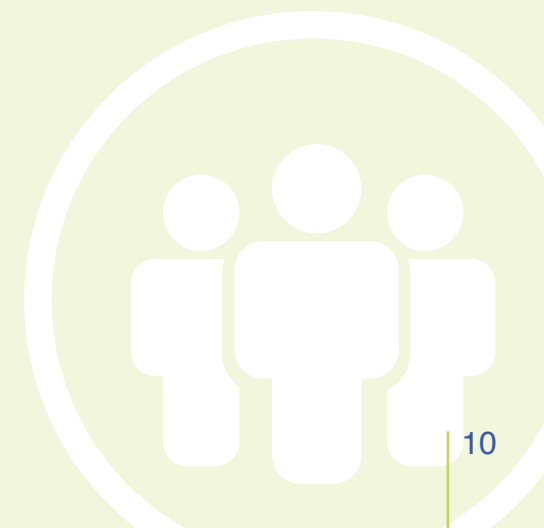
Search Strategy

A scientific search of literature published from January 1, 2018, to June 30, 2022, was conducted. A PRISMA flowchart of the entire study selection process is contained in Figure 1. Bibliographic databases searched include PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Embase. Search terms were adapted for use in each database targeting tick-borne diseases and associated illnesses (e.g., AGS) in the United States. Using the search strategy identified, 1,194, 1,322, and 2,612 articles in the PubMed, CINAHL, and Embase databases, respectively, generated a total of 5,128 total publications. Following removal of duplicates, 4,141 unique articles were screened for eligibility. The title and abstract review removed another 3,519 articles, reducing the total to 622. The full-text review further reduced the total to 321 published articles. Importantly, to validate the final list of included articles, the published included articles were compared to the citations in the 2018–2022 Working Group subcommittee reports as a tool to screen for potentially missed publications. Interestingly, 17% of those articles were previously cited in a Working Group document; thus, 83% of identified literature is novel to this report.

The intent of a grey literature search is to provide a thorough representation of the tick-borne diseases literature and reduce reporting biases (Balshem et al., 2013). Sources were identified using key search terms in Clinicaltrials, Biorxis, Google Scholar, EBSCOhost (OpenDissertations), and Web of Science. Word term searches replicated those used in the published literature review, with appropriate modifications. For example, within Google Scholar, the phrases “tick-borne disease thesis” and “tick-borne disease dissertation” were used to identify relevant unpublished theses and dissertations. Findings are illustrated in the PRISMA flowchart in Figure 1.

The grey literature search consisted of two stages. The first stage involved review of the title, abstracts, and/or descriptions of unpublished dissertations and theses; registered clinical trials; preprints; and conference proceedings. Using an established grey literature search framework (Sadeghieh et al., 2020), database searching continued until five pages of results appeared in succession without new literature appearing. The second stage involved evaluation of each source and modification to the exclusion criteria to ensure that selected studies met the purpose of the review. Also excluded were clinical trials that had been terminated, suspended, or withdrawn and research program budgets. The grey literature search yielded 123 sources, bringing the total number of included sources to 443.

It should be noted that the additional records identified through other searching included 42 state reports. Although not discussed in this chapter, select state reports retrieved were used to inform the reporting of state data in Chapter 4.



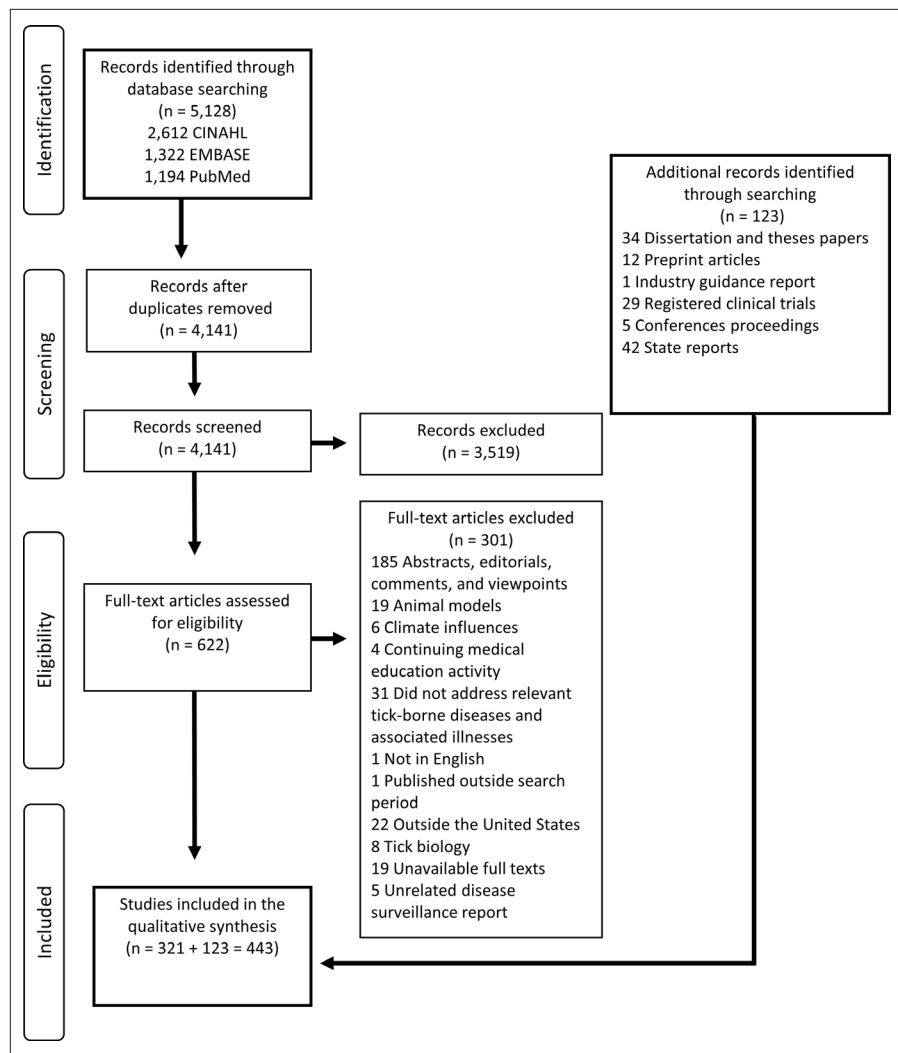


Figure 1. PRISMA flowchart of study selection process.

Findings: Published Literature

The primary objective of the scoping review was to obtain a “bird’s eye view” of published literature pertaining to tick-borne diseases and associated illnesses in the United States. The review focused on examining the extent, range, and nature of research activities of tick-borne diseases and associated

illnesses and identifying existing research gaps. Primary and recurrent themes were documented, and the frequency of publications for each tick-borne disease and associated illness, as well as total publications per year from January 1, 2018, to June 30, 2022, were cataloged.

Apart from 2019, publications have increased year over year (Figure 2). Over the 4.5-year period, 2019 had the fewest number of publications (58), and 2021 had the largest number (80). It is also noteworthy that research shutdowns caused by the COVID-19 pandemic do not seem to have hampered researchers' ability to publish articles during 2020, 2021, and the first half of 2022. The number of published articles by the end of 2022 is projected to exceed the total in 2021, continuing this increasing trend in publications over time.

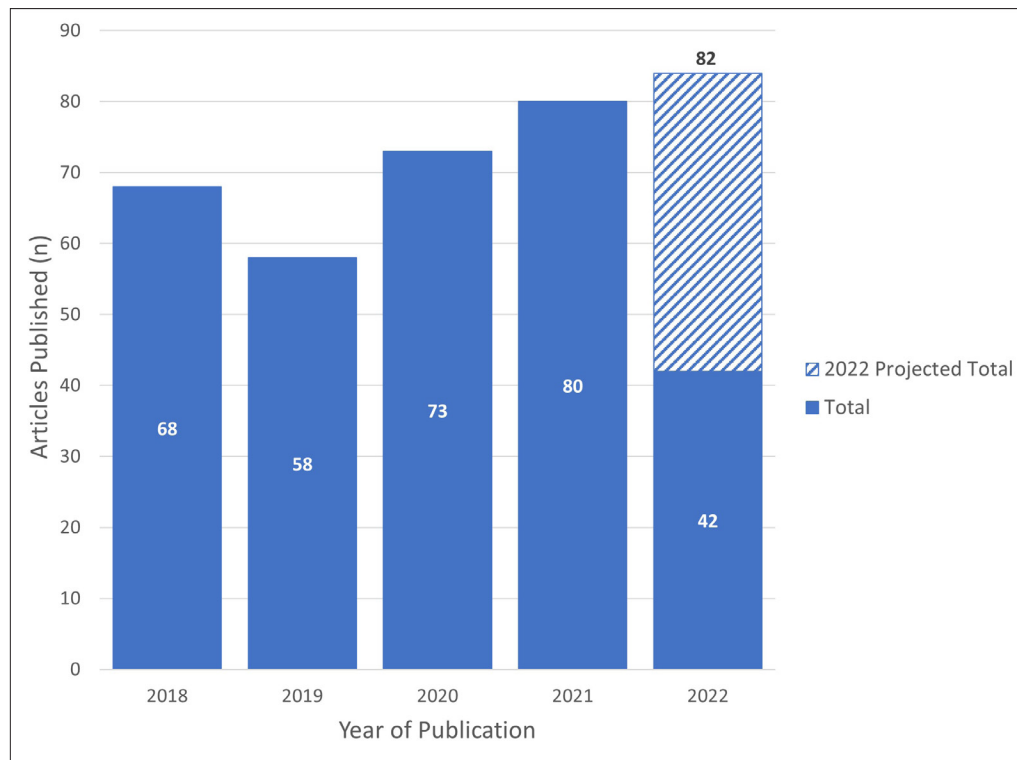


Figure 2. Tick-borne disease articles published from January 1, 2018, to June 30, 2022. Projected 2022 total articles published is represented with diagonals.

Figure 3 details the frequency by category that emerged from the published literature. More than 100 of the 321 articles (31%) reported on the diagnosis of tick-borne diseases and associated illnesses. Twenty-



nine percent of studies ($n = 94$) focused on surveillance of human disease. Articles discussing diagnostics and prevention accounted for 12% ($40/321$) and 12% ($37/321$), respectively. In addition, tick surveillance accounted for 8% ($26/321$) of published articles. Finally, fewer articles (<10 per category) examined clinical presentation, pathogenesis, and treatment of tick-borne diseases and associated illnesses. A catalogue of included publications categorized by theme is provided as supplementary material in the appendices (Appendix F).

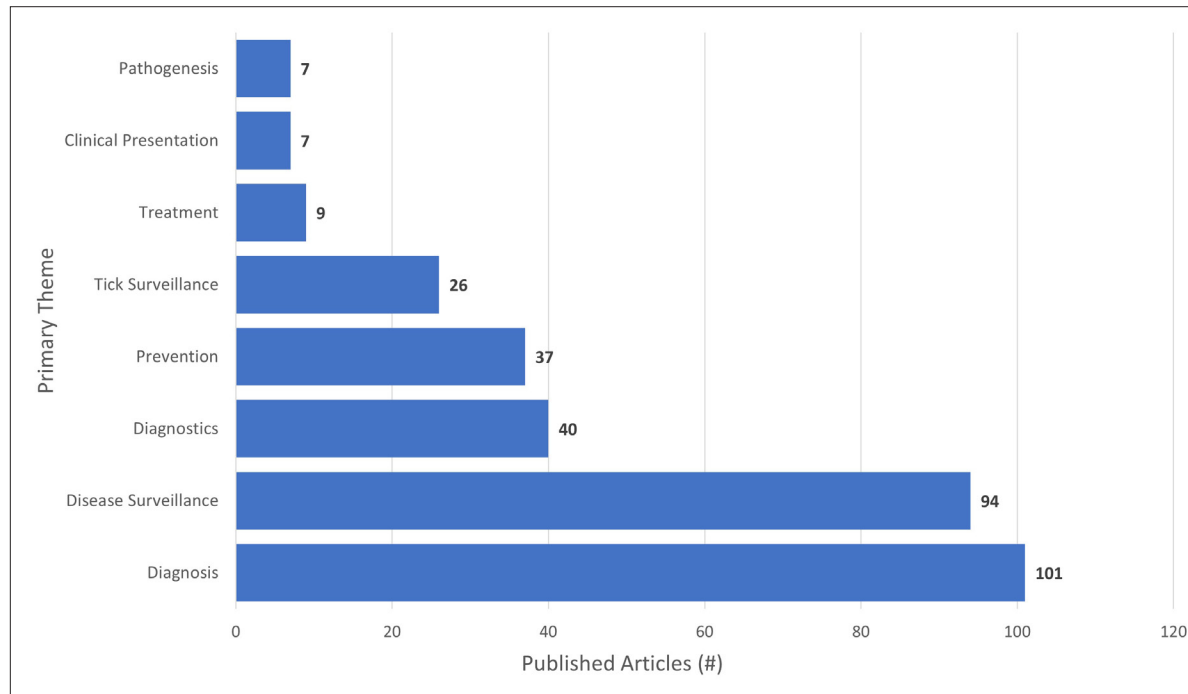


Figure 3. Primary themes of literature published from January 1, 2018, to June 30, 2022.

Figure 4 presents number of publications by tick-associated disease that were captured in the search. Publications related to Lyme disease accounted for greater than 40% ($132/321$) of the total number of publications. The remaining 60% of articles ($189/321$) pertains to 11 other tick-associated illnesses, including babesiosis, anaplasmosis, Powassan virus, spotted fever group rickettsioses (including RMSF and *Rickettsia parkeri* rickettsiosis), AGS, ehrlichiosis, Heartland virus, tick-borne relapsing fever, Bourbon virus, and STARI. Although the goal was to capture research pertaining to any tick-associated disease, articles pertaining to filariasis, Q fever, typhus, and tularemia satisfied the inclusion criteria. Quantifiably, the disparity between the publications researching Lyme disease versus other tick-borne diseases shows the gap in research emphasis.



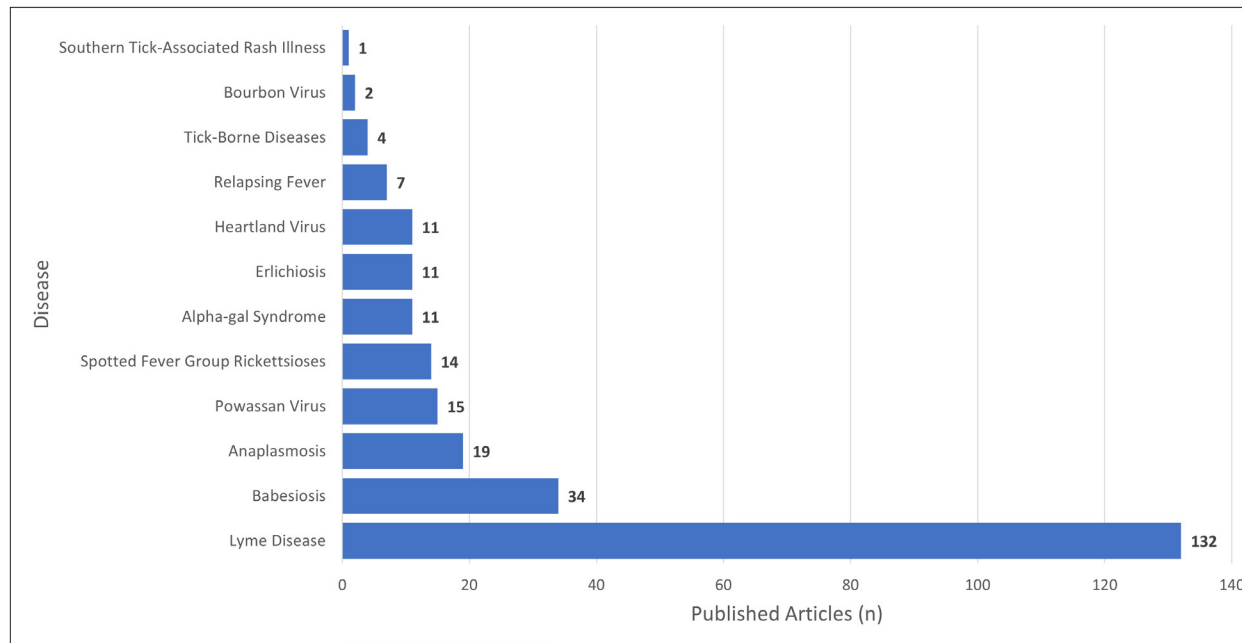


Figure 4. Total number of articles describing tick-borne diseases published from January 1, 2018, to June 30, 2022.

Most of the published research were case studies or reports and publications reporting on surveys (Figure 5). The survey category included disease surveillance and monitoring programs, disease prevalence surveys, tick-borne diseases and associated illnesses, education surveys, and tick surveillance. One-third (38/101) of case studies or case reports described Lyme disease, followed by babesiosis (14/101), anaplasmosis (13/101), Powassan virus (9/101), AGS (7/101), spotted fever group rickettsioses (6/101), ehrlichiosis (4/101), Heartland virus (3/101), tick-borne relapsing fever (3/101), and STARI (1/101). No case studies were found that reported on Bourbon virus, Colorado tick fever, filariasis, Q fever, tularemia, or typhus.



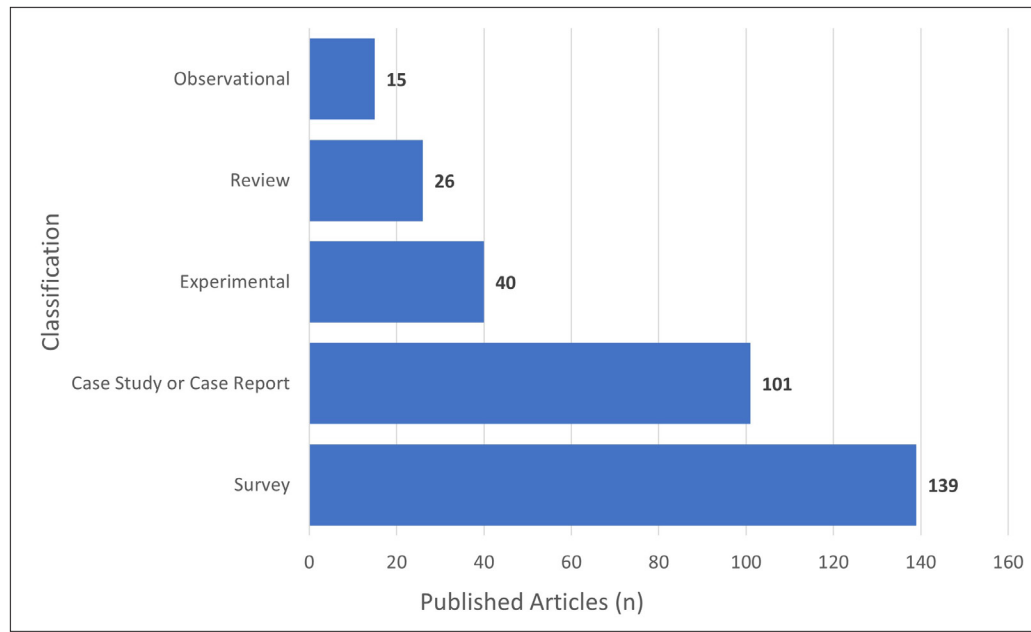


Figure 5. Identified published articles by study design, January 1, 2018, to June 30, 2022.

Findings: Unpublished Literature

Given the vast amount of literature identified in the scoping review, annotated reporting on all publications was not feasible. However, as noted previously, a complete catalogue of literature is contained in the report appendices for reference (Appendix F). Like published literature, the amount of unpublished literature has also increased steadily since 2018. The frequency of unpublished literature by category and type is illustrated in Figure 6. This is followed by a synthesis of the unpublished literature that highlights in-progress, or not-yet published research, including clinical trials, conference proceedings, and industry guidance. Organized by search parameters and themes established at the outset of the inventory, the discussion highlights emerging and potentially impactful research topics. Such topics include surveillance, provider education and awareness, prevention, access to care and disease burden, treatments, diagnosis/diagnostics, disease presentation, and pathogenesis. When relevant as a means to highlight specific issues, published literature is included in the discussion. Highlighting emerging research serves to illustrate the current direction of tick-borne disease research progress broadly.



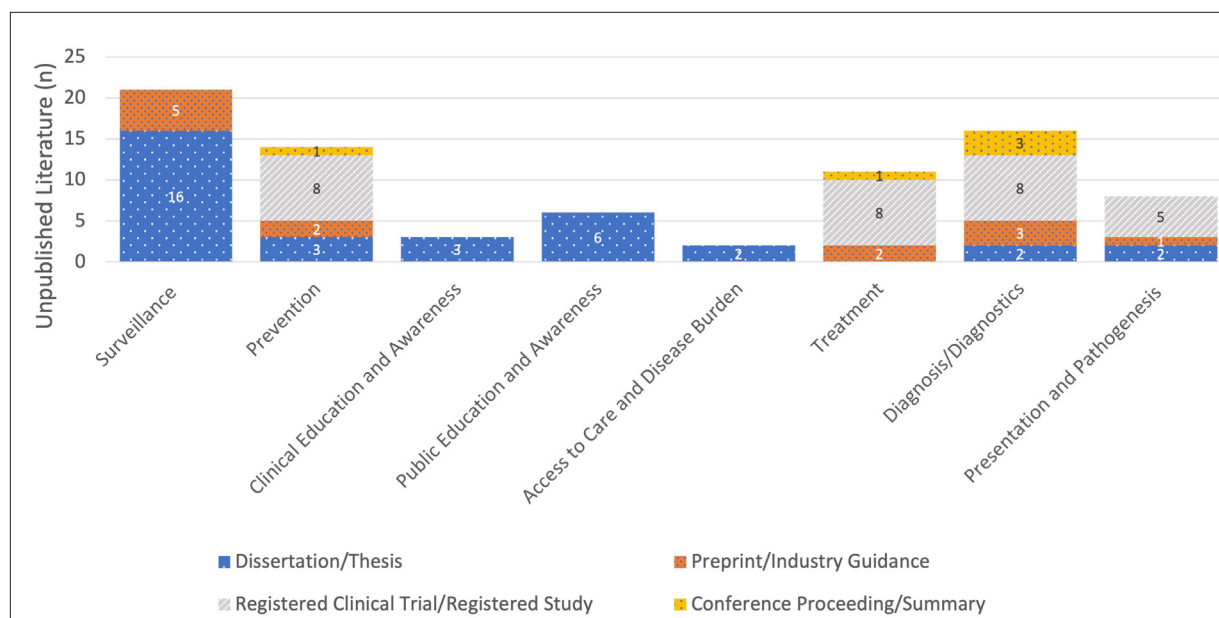


Figure 6. Total number of unpublished literature by category and type, January 1, 2018, to June 30, 2022.

Surveillance

Surveillance of ticks and the pathogens they carry enables the assessment of human risk. Tick surveillance can be conducted actively (e.g., by collecting ticks) or passively (e.g., by analyzing tick samples submitted for testing). As a complement, surveillance of reported human disease cases offers insight into the incidence of illness in different regions, also an indicator of potential risk. The surveillance of ticks, their pathogens, and the incidence of human disease represent important public health tools. They yield data that can be used to better understand the burden of illness and to prevent transmission of pathogens to people in areas of higher risk.

The creation of tick maps as a tick surveillance tool in both endemic and non-endemic areas is valuable for identifying and tracking tick risk areas. In an unpublished dissertation (Phillips, 2020), surveillance efforts were used to create distribution models of lone star ticks (*A. americanum*) and American dog ticks (*Dermacentor variabilis*). The models were used to identify environmental influences on tick populations and to inform public health officials about where prevention measures should be targeted. In addition, Bingham (2022) created a risk map for Lyme disease across the continental United States using multiple tick- and human-related factors, including the presence of tick species in different areas, human social behaviors, and land use management.



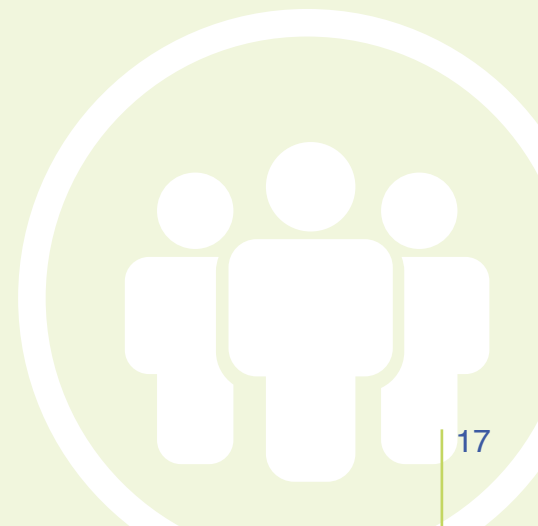
Surveillance also provides insight into tick concentrations (Adams, 2022) and changes in tick distribution patterns (Lyons, 2022; Thornburg, 2021) in different landscapes (e.g., grassland) and location types (e.g., residential versus non-residential). Examples of such surveillance can be seen in theses by Alzahrani (2018) and Small (2018), who investigated distributions of tick species based on the type of land and location. This type of surveillance data enables public health officials to better determine when and where protective measures should occur.

The search of unpublished literature revealed a novel tick surveillance and identification method involving the use of photographs. In a 2020 dissertation, Kopsco explored the use of TickSpotters, a national photograph-based tick surveillance platform, as an alternative passive surveillance method. Here, the researcher compared the photograph submissions to TickSpotters with nationwide existing county reports of *Ixodes scapularis*, *Ixodes pacificus*, and *A. americanum*. Results revealed that greater than 50% of photographs submitted by citizens to TickSpotters corresponded to the distribution of ticks.

Human surveillance can identify areas of emerging risk and prevent missed diagnoses in non-endemic areas. Employing a predictive modeling approach, Brummitt (2021) used automatically reported lab reports and demographic risk factor information (age, sex) to predict underestimated Lyme disease cases in low-incidence areas of California. Human surveillance efforts are also beneficial for identifying high-risk populations. For example, Eisenstein (2020) analyzed human granulocytic anaplasmosis cases in Connecticut from 2014 to 2019 and found that most cases occurred in males aged 50–59. In addition, Ashraf (2020) determined that lower median income and residence in non-metropolitan counties were significant predictors of acquiring Lyme disease, babesiosis, and anaplasmosis.

Osborne (2018) described tick surveillance in Fresno and Madera counties of California, which led to the identification of *R. parkeri* in a group of *Ornithodoros parkeri* ticks. Though non-pathogenic, the pathogen had not yet been detected in this tick species. Similarly, the Gulf Coast tick (*Amblyomma maculatum*) was identified in New Jersey and parts of New York, suggesting an emerging presence of this species in the area (Bajwa et al., 2022). A preprint article that assessed the prevalence of viruses in ticks in St. Louis County, MO, found that some of the lone star ticks (*A. Americanum*) collected for the study tested positive for Bourbon and Heartland viruses (Aziati et al., 2022). Importantly a preprint article by Fowler et al. (2022) identified an established population of lone star ticks in Southern Michigan, suggesting that this tick species is expanding its range into that region. Initial evidence of established populations of lone star ticks has also been identified for the first time in eastern South Dakota (Black, 2022).

Taken together, the unpublished literature demonstrates the importance of ongoing surveillance and novel surveillance methods, in endemic and non-endemic tick-borne disease areas. This research identifies emerging risk areas and high-risk groups, which is necessary for establishing preventative measures and is critical to the safety of at-risk populations.



Public Education and Awareness

Reducing transmission of tick-borne diseases requires a multi-pronged approach. To increase awareness and successful uptake of preventative measures within the general population, public health officials should improve public education of tick-borne diseases and associated conditions and broaden the disease acumen of health care professionals through education and state-of-the-art research.

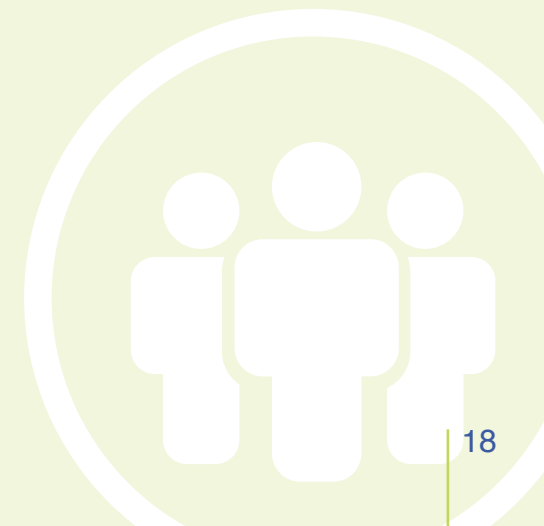
The grey literature indicates that a perceived risk of tick-borne disease predicts whether individuals will take precautionary measures against tick bites, such as conducting tick checks. However, research findings suggest a disconnect between perceived and actual risk (Butler, 2019; Hassett, 2020). Although knowledge of risk plays a key role in predicting the use of precautionary measures (Cuaderna, 2021; Hassett, 2020), it is not a clear predictor. For example, studies of outdoor recreationists in Maine and residents in transboundary regions of the United States and Mexico found that knowledge did not predict prevention measures (Aguilar, 2021; Perry, 2021). However, research suggests that direct exposure to tick-borne diseases affects behavior. Hassett (2020) reported that park visitors in Long Island, NY, with a household member previously diagnosed with a tick-borne disease were more likely to seek medical care following a tick bite. Of note, 43% of people in the sample believed that most tick bites occur in parks, and 43% believed that their risk of exposure to a tick was minimal (Hassett, 2020).

Given the knowledge gaps concerning tick-borne diseases, the field should develop and measure effective public education tools. A registered clinical trial demonstrated the success of an educational intervention among children aged 7–12 in schools located in Lyme disease–endemic areas. In a pre-post knowledge assessment, results revealed that students' composite knowledge regarding Lyme disease and risk improved after the intervention. Thus, providing education for young school-aged children may improve awareness of tick-borne disease (Shadick, NCT00594997).

Clinician Education and Awareness

Like public knowledge, clinician knowledge is critical to tick-borne disease prevention. One unpublished study surveyed health care providers working in schools in the Lyme disease–endemic areas of New York State and Maryland. Findings demonstrated a knowledge gap, with only 52% ($n = 1,560$) of clinicians receiving a passing score on the knowledge index. Predictors of a passing score were experience with ticks and tick-borne diseases, perceived risk, and confidence in treating tick bites and tick-borne diseases (Howard, 2020). Of note, these findings were consistent with the data regarding individuals' knowledge and preventative measures discussed above; that is, when one's perceived risk of tick-borne diseases increases, the likelihood of taking precautionary measures also increases.

In another study, Kaur (2021) surveyed health care providers in Indiana and identified knowledge gaps related to tick-borne diseases. The results showed that respondents knew little about tick species disease



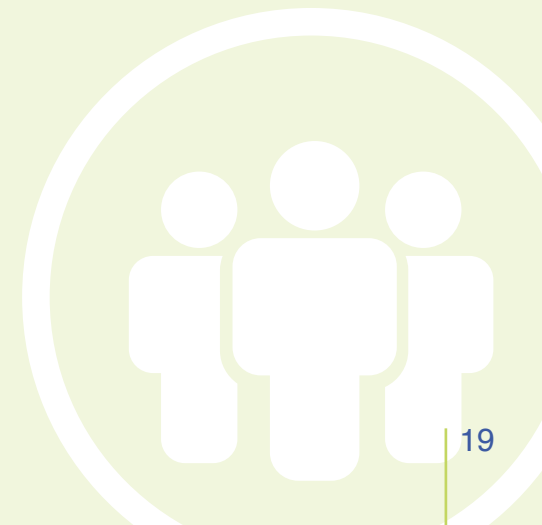
transmission in Indiana, the regional prevalence of the black legged tick (*Ixodes scapularis*), the high risk of Lyme disease in northwest Indiana, or the months with the highest tick-borne disease transmission. Increased education of health care providers is critical to closing these knowledge gaps. Blanken-Little (2021) designed a webinar to educate registered and advanced practice registered nurses about tick-borne diseases. A knowledge assessment was administered before and after the nurses viewed the webinar. The results revealed that the webinar increased general knowledge about Lyme disease and its treatment. Improvement was noted in provider knowledge of endemic areas, seasonal risk, time spans between tick attachment and the presentation of early localized Lyme disease symptoms, treatment options for pregnant or lactating people, and prevention measures.

Prevention

Prevention measures expand beyond public and clinician awareness of disease. Currently, no tick-borne disease vaccine is available for human use. LYMErix, an earlier Lyme disease vaccine, was available from 1998 to 2002 but was withdrawn from the market (Comstedt et al., 2017). However, Pfizer has recently announced the launch of a Phase III trial of the vaccine VLA15, a multivalent recombinant protein vaccine that targets the outer surface protein A (OspA) of *B. burgdoferi*, the bacteria that causes Lyme disease (Pfizer, NCT05477524). OspA is a surface protein expressed by the bacteria when present in a tick. Blocking OspA inhibits the bacteria's ability to leave the tick and infect humans. The trial will help determine the reduction in confirmed Lyme disease cases in participants receiving VLA15 compared to the placebo control group. Endpoints include local reactions, systemic events, adverse events, and newly diagnosed chronic medical conditions following vaccination. Measurement of vaccine efficacy will occur at 1 month following vaccination series and at 1 year following a booster dose. If successful, the VLA15 vaccine would be a critical step in reducing the incidence of Lyme disease globally.

Much prevention research is primarily focused on a Lyme disease vaccine. However, an ongoing Phase II clinical trial by the U.S. Army Medical Research and Development Command is studying the safety and immunogenicity of the live, attenuated tularemia vaccine (U.S. Army Medical Research and Development Command, NCT 00584844). In addition, another trial is evaluating the long-term immunogenicity effects (up to 10 years after booster dose) of a vaccine developed for tick-borne encephalitis (TBE) (GlaxoSmithKline, NCT01562444).

Obstacles to the uptake of vaccines include vaccine access and hesitancy. Hook (2021) investigated the cost of illness of Lyme disease, people's willingness to be vaccinated, and the cost of vaccination. The researcher found that the average out-of-pocket costs (direct and indirect) attributable to Lyme disease for all study participants with Lyme disease was \$1,340. With productivity losses factored in, the average total cost was \$2,270. Stratified analyses by disease category revealed that the cost for participants with



disseminated Lyme disease was double that of participants with localized Lyme disease. To evaluate people's willingness to be vaccinated, a web-based survey was delivered to a unique random sample of people living in Lyme disease–endemic states. This sample of people were not privy to information in the cost of illness portion of the study. Survey results indicated that 64% of respondents were willing to receive a Lyme disease vaccine, 30% were uncertain, and 7% were unwilling to receive a Lyme disease vaccine. Respondents who were uncertain were more likely to be parents, aged 45–65 years, and non-White; hold less than a bachelor's degree; and have concerns about the safety of a Lyme disease vaccine. The cost-benefit analysis revealed that vaccinated individuals would incur a net cost of \$150 over a 3-year period of vaccine effectiveness but could save money when Lyme disease cost-of-illness was considered.

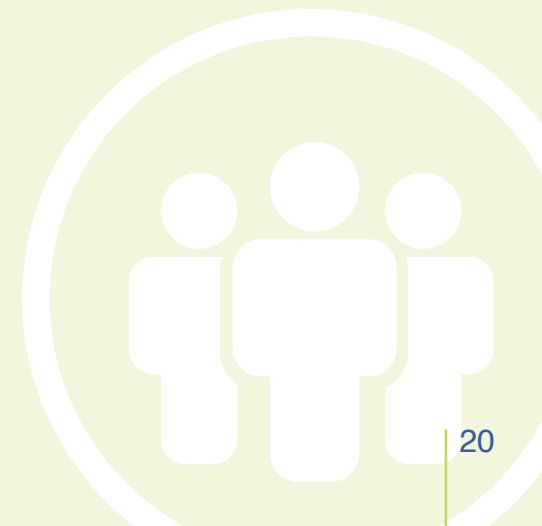
An important element of reducing transmission of tick-borne disease involves the control and reduction of tick populations. Areas of current unpublished research in tick-borne disease prevention include spatial repellency, controlled forest burning and thinning, and robotic control of tick populations.

Spatial repellency uses contact repellants to reduce the host-seeking behavior of ticks; however, its effectiveness is difficult to measure. A new method, termed Vertical Tick Assay for Evaluation of Spatial Repellents (VTA-ESR) evaluates host-seeking tick behavior following exposure to chemical repellents (Siegel et al., 2022). A study of its efficacy revealed that when American dog ticks (*D. variabilis*) and lone star ticks (*A. americanum*) were exposed to the chemical repellents, metofluthrin and transluthrin, they demonstrated a strong reduction in host-seeking activity; however, blacklegged ticks (*I. scapularis*) were slightly less affected by repellants (Siegel et al., 2022).

The use of permethrin-treated clothing is known to prevent bites from lone star ticks; however, one study found that permethrin loses effectiveness on clothing after 1 year (UNC, Chapel Hill, NCT01454414). A registered clinical trial is investigating permethrin's protective qualities against blacklegged ticks as well as the causes of decreased effectiveness (UNC, Chapel Hill, NCT02613585).

Forest burning and thinning is another method to reduce tick bites. Newman (2021) found that the combination of forest burning and thinning successfully decreased the population of lone star ticks (*A. americanum*) and potentially decreased the incidence of spotted fever group rickettsioses. A study investigating robotic control of tick populations showed that a permethrin-treated robot onto which ticks would latch reduced the tick population by 88% immediately after treatment. The permethrin-treated robot left little to no traces of permethrin in the environment. However, 48 hours after treatment, the tick population returned to pre-treatment levels (Celentano et al., 2020).

One emerging Lyme disease prevention method that could offer immediate protection is injection of antibodies designed to prevent transmission of *Borrelia* spirochetes. An ongoing Phase I randomized,



partial-blind, placebo-controlled clinical trial by MassBiologics aims to evaluate the safety of the use of a human antibody, 2217LS, to protect against Lyme disease. Endpoints include safety and tolerability of subcutaneous injection of 2217LS as well as the quantity of the antibody in the participants' blood following injections (MassBiologics, NCT04863287).

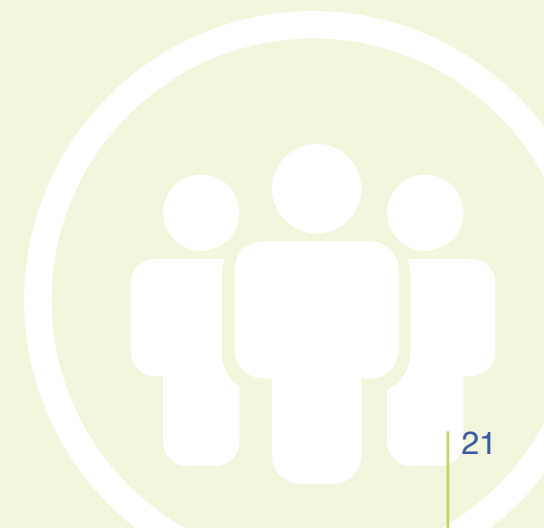
Access to Care and Disease Burden

Tick-borne diseases can have negative long-term effects on the health and quality of life (QoL) of affected individuals. Two unpublished studies have analyzed the burden of Lyme disease and RMSF. One dissertation evaluated barriers to care and their impact on the QoL of 406 women with Lyme disease–associated chronic illness (Jones, 2022). Data collection occurred via a survey (n = 373), group discussion (n = 11), and written narratives (n = 22). Participants reported several barriers to appropriate care, including difficulty receiving a timely diagnosis, receiving appropriate treatment, and finding and paying for treatment. In addition, participants reported negative impacts of disease on their personal and professional lives, including relationship stress and reduced ability to work. Finally, in the focus group and personal narratives, participants reported that health care providers trivialized, dismissed, and disbelieved their concerns and symptoms.

To better understand the long-term impacts of RMSF, Drexler (2020) followed a group of 80 individuals hospitalized for RMSF in two Arizona tribal communities from 2002 to 2017. The researcher aimed to investigate the presence, persistence, and cost of long-term sequelae from RMSF. The findings revealed that delayed antibiotic therapy was the strongest predictor in the 23% of participants who displayed signs of long-term sequelae from RMSF. The study also estimated the total disease impact of long-term sequelae from RMSF based on disability-adjusted life years (i.e., the years of life lost to premature mortality combined with years of healthy life lost to disability). In the group studied, the estimated impact of the disease was 516 disability-adjusted life years lost from 2002 to 2017, a substantial impact to these small tribal communities (Drexler, 2020).

Taken together, these two studies underscore the importance of proper and timely treatment for tick-borne disease. Both studies demonstrate that participants experienced complications from delayed diagnosis and treatment of tick-borne disease. Critically, delayed diagnosis leads to serious long-term consequences for some individuals, impacting their daily lives, and in some cases, causing premature mortality. Reducing the access to care gap would reduce the undue burden on individuals and their communities. It is important to understand the burden of tick-borne disease to better guide medical treatment and policy to help avoid these long-term consequences.

Previous estimates show that 10–20% of Lyme disease patients make a full recovery (Marques, 2008); however, as many as 35% of patients endure long-term, debilitating illness (Aucott et al., 2013). Two



ongoing clinical trials are investigating the use of tetracycline therapy and disulfiram for Lyme disease–associated chronic illness (Johns Hopkins University, NCT05219929; Fallon, NCT03891667). Although tetracyclines (e.g., doxycycline) are used to treat Lyme disease, no clinical trials have evaluated the treatment of extended tetracyclines (> 4 weeks), for Lyme disease–associated chronic illness. A clinical trial is comparing symptom reduction in individuals treated with a tetracycline compared to a placebo following 3 months. Based on this drug’s anti-inflammatory properties and effectiveness in treating other diseases, researchers hypothesize that patients with prolonged Lyme disease symptoms will experience improvements in fatigue, symptom burden, and functional impact following treatment (Johns Hopkins University, NCT05219929). A second trial investigating disulfiram as a treatment for Lyme disease–associated chronic illness is based on earlier success (Fallon, NCT03891667).

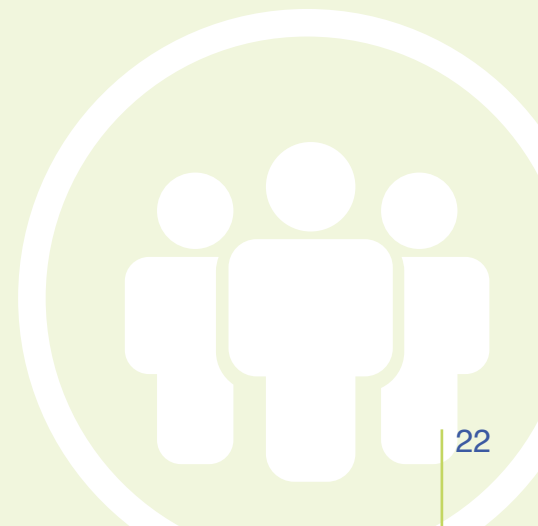
Three unpublished studies are evaluating the use of medications currently used to treat other ailments to treat Lyme disease. One ongoing clinical trial is investigating the use of non-steroidal anti-inflammatory drugs (NSAIDs) to treat Lyme arthritis (Neville, NCT04038346). Another study has demonstrated that nitroxoline (an antibiotic currently used to treat urinary tract infections), in combination with other drugs, is effective in eradicating most of the Lyme disease–causing bacteria (98.3%), in-vitro (Alvarez-Manzo et al., 2021). Finally, as discussed during the Global Lyme Disease Alliance conference in 2018, researchers are investigating the use of hygromycin A to eradicate *B. burgdorferi* (Leimer et al., 2021).

Studies of non-pharmaceutical treatments for Lyme disease–associated chronic illness include investigations of the use of acetogenins and a novel Nutraceutical (Optimal Health Research, NCT04078841; NCT04141969). These exploratory studies are completed; however, findings are not yet available. For example, one alternative treatment for Lyme disease is tele-yoga. A pre-post study to measure the effectiveness of tele-yoga to treat Lyme disease symptoms over a 12-week treatment period is under way (Bayley, NCT04867473).

Diagnosis and Diagnostics

The grey literature identified unpublished research related to diagnostics, including the development of improved diagnostic tests for Lyme disease and the identification of unique biomarkers and signatures of Lyme disease and Lyme disease–associated chronic illness. Currently available Lyme disease diagnostic tests (standard 2-tiered approach) recommended by CDC require the use of two immunoassays, making them labor intensive. These tests detect a host-antibody response, which may require more than 3 weeks to develop (Siddarth, 2022). Thus, these tests are slow, lack specificity, and are not sensitive to early-stage infections (Chou et al., 2019; Siddarth, 2022).

Delayed testing leads to delayed treatment. Therefore, novel diagnostic tests are being developed to increase the accuracy and specificity of detection of Lyme disease at both the early and late stages.

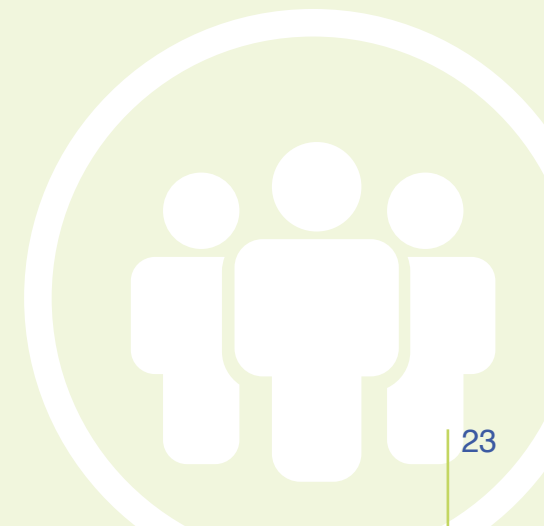


Several of these tests detect antibodies for *B. burgdorferi* proteins (i.e., GC-FP, MicroB-plex, and digital polymerase chain reaction [PCR] tests). The MicroB-plex Lyme test is designed to test for Lyme at its earliest stages, enabling earlier treatment (MicroB-plex, Inc., NCT03963635). Other tests, such as Grating Coupled-Fluorescent Plasmonic (GC-FP), have demonstrated the ability to distinguish between early and disseminated Lyme disease and may be more sensitive than the western blot approach (Chou et al., 2019).

A diagnostic test that appears to be more sensitive than current tests is next generation sequencing. Potentially more accurate than current PCR tests, next generation sequencing can sequence millions of small stands of DNA, whereas PCR tests can only detect larger DNA strands (Beneri, NCT03505879). Siddarth (2022) has designed a novel standalone multiplexed sandwich ELISA assay as a point-of-care Lyme disease diagnostic. Even though this test uses a single assay, it is equally specific but more sensitive than the standard two-assay tests. Further, it enables more rapid testing of patients for Lyme disease.

Current research is exploring the identification of biomarkers in individuals with Lyme disease (FlightPath Biosciences, Inc., NCT04835792) and Lyme disease–associated chronic illness (Landa, 2022). By testing stool and blood samples, researchers can search for unique biomarkers based on the microbiome, transcriptome, and metabolome of individuals with Lyme disease–associated illness compared to healthy individuals (FlightPath Biosciences, Inc., NCT04835792). Researchers have also used imaging to search for hypothesized hyper-activated brain networks, thought to cause increased sensitivity to pain in individuals with Lyme disease–associated chronic illness (Landa, 2022). In addition, as discussed during the Global Lyme Alliance conference in 2018, researchers are studying metabolic signatures for Lyme disease to provide additional Lyme disease biomarker information (Global Lyme Alliance, 2018).

Identification of additional biomarkers can help distinguish between localized and disseminated Lyme disease, and between features of inflammatory responses in Lyme disease compared to other inflammatory diseases (Fatou et al., 2020; Haslund-Gourley et al., 2022). Fatou et al. (2020) examined the serum proteome of individuals with localized or disseminated Lyme disease. Then they identified specific pathway activation associated with localized versus disseminated Lyme disease. They also identified a potential candidate biomarker specific to disseminated Lyme disease, that is, members of the serum amyloid A protein family (Fatou et al., 2020). Although this research is preliminary, findings demonstrate advances toward distinguishing the progression of Lyme disease. In another study, Haslund-Gourley et al. (2022) aimed to characterize the glycoprotein Immunoglobulin G (IgG) N-glycan response to Lyme disease. They found that the IgG N-glycan signatures of Lyme disease were significantly different from those associated with most diseases that result in an inflammatory response. This finding further supports



evidence that IgG N-glycan signatures in Lyme disease are a unique biomarker that could be used to diagnose the disease (Haslund-Gourley et al., 2022).

Presentation and Pathogenesis

Previous animal studies have indicated that xenodiagnosis is effective in identifying *B. burgdorferi* (Hodzic et al., 2014). This method uses laboratory-bred ticks to detect Lyme disease bacteria. To better understand post-treatment Lyme disease, an ongoing clinical trial plans to use xenodiagnosis to identify *B. burgdorferi* in individuals who have previously received antibiotic treatment for Lyme disease. Researchers hope to determine whether lasting *B. burgdorferi* after treatment is more common in individuals who experience post-treatment Lyme disease (National Institutes of Health Clinical Center, NIAID, NCT02446626).

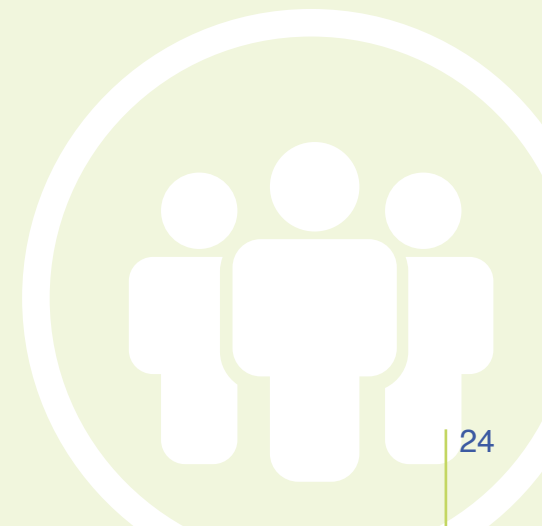
Currently, little is known about the lipid receptors that detect the presence of *B. burgdorferi* in ticks and humans. O'Neal et al. (2022) have identified a superfamily of lipid receptors, CD36, that are critical for the immune function against Lyme disease. Their study results showed that, in both humans and ticks, CD36 molecules are the immune receptors that recognize *B. burgdorferi*. Investigation of CD36 genes in a biobank revealed that Lyme disease diagnosis was associated with a loss-of-function variant in the CD36 gene in humans. Thus, researchers conclude that the CD36 superfamily likely provides resistance against *B. burgdorferi* infection (O'Neal et al., 2022)

In addition, an ongoing study uses a unique investigational-use blood test, T-detect Lyme, to test T-cells for an adaptive immune response to Lyme disease (Adaptive Biotechnologies, NCT04422314). This study may be beneficial in two ways. First, the test may provide a better understanding of the human immune response to Lyme disease because of its unique ability to test T-cells. Second, the test may demonstrate fully accurate and specific diagnostics for Lyme disease, which will improve the diagnostic process (Adaptive Biotechnologies, NCT04422314).

Current immunology research aims to understand the human immune response in skin and blood following tick bites. In furtherance of this goal, a research team plans to expose humans to tick bites in a controlled laboratory setting and then compare skin biopsies between intervention and control groups to identify tick salivary proteins targeted by the host immune response. Participants will also report symptoms (e.g., itching at the bite sites) and provide blood samples. Results could aid in the development of an anti-tick vaccine. This trial is currently in the recruiting phase, with an estimated completion date of June 2023 (National Institutes of Health Clinical Center, NIAID, NCT05036707).

Health Equity

The 2022 Working Group identified equity as a significant issue within the tick-borne diseases landscape (Access to Care and Education Subcommittee, 2022; Changing Dynamics of Tick Ecology, Control, and

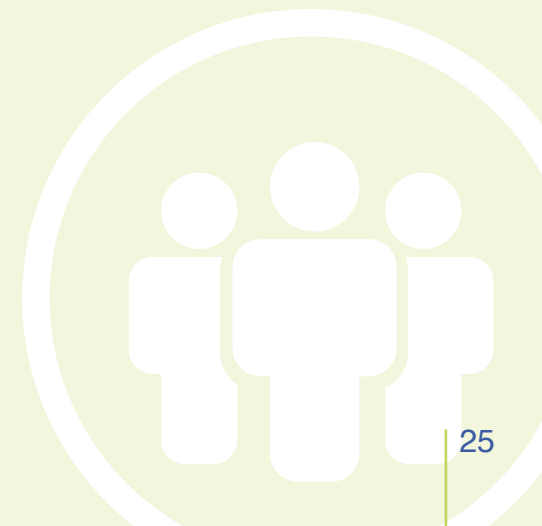


Personal Protection, 2022; Clinical Presentation and Pathogenesis, 2022). Complex health issues such as tick-borne diseases are susceptible to the effects of societal barriers that impede access to care. All efforts to address tick-borne diseases should be rooted in the universal recognition that social determinants of health can significantly exacerbate health inequities. Consequently, this report dedicates a stand-alone discussion of the issue of equity that draws on published literature identified from the scoping review.

Several studies examined gendered variations in response to tick exposure, likelihood of being diagnosed with a tick-borne disease, and adoption of personal preventative measures (Baker et al., 2020; Brummitt et al., 2020; Krow-Lucal et al., 2018; Kugeler et al., 2021b; Kuriakose et al., 2020; Liu et al., 2019; Mogg et al., 2020; Shen et al., 2021). Studies have identified that males are significantly more likely to be diagnosed with tick-borne diseases such as Lyme disease, ehrlichiosis, anaplasmosis, Powassan virus, and babesiosis (Baker et al., 2020; Brummitt et al., 2020; Krow-Lucal et al., 2018; Kugeler et al., 2021b; Kuriakose et al., 2020). Surveys seeking to identify behavioral trends observed gender differences in response to tick exposure, preventative methods, and emotional responses. Generally, males were more likely to report diagnosis with a tick-borne disease and tick encounters (Omodior et al., 2019, 2021). However, males were also more likely to report decreased practice of personal protective measures such as tick checks following outdoor exposure and decreased usage of chemical repellents. Nevertheless, males also reported less avoidance of the outdoors in response to concerns over tick exposure than their female counterparts (Omodior et al., 2019, 2021). This finding indicates a potential disconnect between perception of personal risk due to tick-borne diseases, tick exposure, and adoption of personal protective measures. Decreased risk perception combined with decreased preventative measures is likely a driving factor in the increased risk of males to present with tick-borne diseases.

Children and older adults are particularly at risk of tick exposure, tick-borne diseases, and increased complications associated with tick-borne diseases. Certain tick-borne diseases affect age groups differently. Clinical and self-reported surveys identified that older adults are at particular risk of diagnosis with ehrlichiosis (Brown Marusiak et al., 2022; Kuriakose et al., 2020), babesiosis (Liu et al., 2019), and Powassan virus (Krow-Lucal et al., 2018). In addition, a clinical review of people in the United States who had contracted Powassan virus between 2006 and 2016 revealed that, although the age at diagnosis ranged from 3 months to 87 years, the median age at diagnosis was 62 years and the only cases observed to result in death were in adults over age 50 years (Krow-Lucal et al., 2018). This finding indicates that older adults historically face greater risks associated from ehrlichiosis, babesiosis, and Powassan virus. Children, however, are at greater risk of developing human granulocytic anaplasmosis (Schotthoefer et al., 2018), and the prevalence of ehrlichiosis in south Texas children has begun to increase (Erickson et al., 2021).

Lyme disease differs from other tick-borne diseases in that its prevalence peaks for both children and older adults, rather than selecting for older adults or children alone. A review of reported cases from 1992

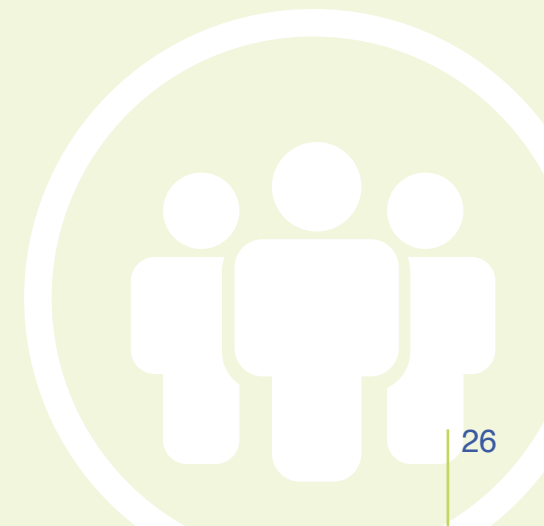


to 2016 revealed that children aged 5–9 years were the most consistently affected age group (Kugeler et al., 2021b). Although recent surveys indicate that Lyme disease exposure in children is increasing (Eddens et al., 2019), research continues to identify older adults as most at risk, particularly those born between 1950 and 1964 (Kugeler et al., 2021b). The dual-population risk for Lyme disease further exemplifies the vulnerability of children and adults to tick exposure and tick-borne diseases.

Trends obtained from citizen surveillance programs have also shown that adults and children are more likely to experience tick exposure (Jordan & Egizi, 2019). Furthermore, ticks obtained from children and adults are more likely to have been fed from the host prior to removal, further increasing the risk of tick-borne disease exposure (Jordan & Egizi, 2019). A separate, app-based tick exposure reporting system reports similar trends of adults over age 50 experiencing higher numbers of tick exposure than other age groups (Fernandez et al., 2019). Children are underrepresented in the data because of the mode of reporting (Fernandez et al., 2019), although children are expected to have a high rate of tick exposure as noted in alternative studies (Jordan & Egizi, 2019). While older adults report a greater likelihood of tick exposure, they also report decreased utilization of tick preventative measures (Nawrocki & Hinckley, 2021) and a decreased willingness to obtain a hypothetical Lyme disease vaccine (Hook et al., 2022).

Although both age groups are vulnerable to Lyme disease, diagnostics, treatment, and self-reported perceptions differ between the two populations. Children and adults report different symptoms and may require different diagnostic methods (Dart et al., 2018; Shen et al., 2021). This may relate to differences in observed health care costs. A study of people hospitalized for Lyme disease and related complications reported that associated costs were greatest for patients aged 15–years (Schwartz et al., 2020).

Surveillance studies suggest that ticks are more abundant in areas with increased forest cover, downed logs, and endemic deer populations (Hahn et al., 2018), suggesting that exposure to rural or natural lands would correlate to increased tick exposure and tick-borne diseases. However, results from clinical and self-report surveys conflict. Several studies indicated that the prevalence of tick-borne diseases such as Lyme disease and babesiosis is higher in rural areas compared to urban communities (Liu et al., 2019; Roome et al., 2022), while alternative studies reported increased rates of ehrlichiosis and RMSF in urbanized counties (Omodior, 2021). Citizen science surveillance reports indicated that people in rural areas are more likely to report observing ticks, finding a tick on their person, and finding ticks on children (Omodior et al., 2021), while self-surveys indicated a high incidence of people reporting ticks around their residences rather than in parks or more natural areas (Jordan & Egizi, 2019; Moon et al., 2019). These differences are likely influenced by differing modes of collecting clinical data and differing likelihoods of adopting personal prevention measures. Clinical reports often utilize hospital records to collect data, which can result in incomplete or biased datasets. People in urban areas are more likely to seek medical

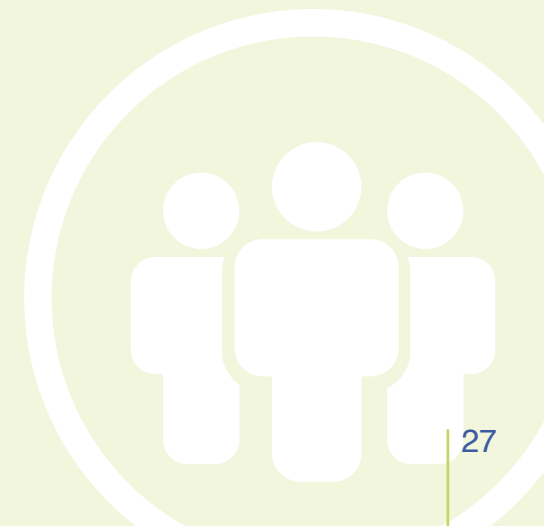


attention in a hospital setting, while people in rural areas are equally likely to present to a hospital or primary care setting (Eddens et al., 2019). Surveys also indicate that people in urban areas are less likely to utilize protective measures than people in rural areas.

Access to care is a major determinant of tick-borne diseases prognosis. Delayed treatment is associated with an increased risk of admission to the intensive care unit and with developing Lyme disease–associated chronic illnesses (Hirsch et al., 2020; Kuriakose et al., 2020). Clinical reports and self-report surveys identify access to health insurance as a driving force behind delays in seeking medical treatment (Hirsch et al., 2018, 2020). Individuals without insurance were most likely to report delays in obtaining health care for suspected Lyme disease infection (Hirsch et al., 2020). Furthermore, people with health care, such as those enrolled in Medicare, were more likely to be diagnosed with babesiosis (Menis et al., 2021), and those with state-administered health care had increased risk of Lyme disease–associated chronic illness (Moon et al., 2021). However, there are inherent biases in research that primarily utilizes health care records and self-report surveys. These studies rely on people’s ability to access health care to receive a diagnosis and require knowledge of tick-borne diseases, both of which may result in underrepresentation of peoples without health insurance (Access to Care and Education Subcommittee, 2022; Hirsch et al., 2018, 2020).

Type of care facility may also influence treatment delays. People in rural areas are equally likely to report to primary care physicians as to hospitals, while patients in urban areas are more likely to acquire health care from hospital settings (Eddens et al., 2019). Research suggests that evaluation in outpatient settings may result in misdiagnosis of Lyme disease and other tick-borne diseases, resulting in delayed treatment and increased hospitalization (Liu et al., 2019; Shen et al., 2021). In one study, of patients with Lyme carditis, 41% of those hospitalized for treatment were initially suspected of having Lyme disease and only 17% received treatment prior to hospitalization (Shen et al., 2021). Lack of patient awareness regarding Lyme disease and other tick-borne disease symptoms is also a factor in treatment delay, because patients may be unaware of the risks of tick exposure and when it is appropriate to seek clinical care (Hirsch et al., 2018).

Lack of access to care caused by financial strain presents an additional barrier to adequate medical care. A survey of the Truven Health Analytics MarketScan Commercial Claims and Encounters Databases, which queried patient costs associated with Lyme disease–associated illnesses, indicated that the median cost of hospitalization in people aged 65 and younger, when adjusted for U.S. dollars in 2016, was approximately \$11,700 (Schwartz et al., 2020). The median costs were incurred for treatment of Lyme disease–associated carditis, meningitis, arthritis, and facial palsy, in that order. Furthermore, people aged 15–19 experienced the greatest median cost of any age group surveyed, likely as a result of having high rates of meningitis while also experiencing a range of other Lyme disease–associated chronic illnesses



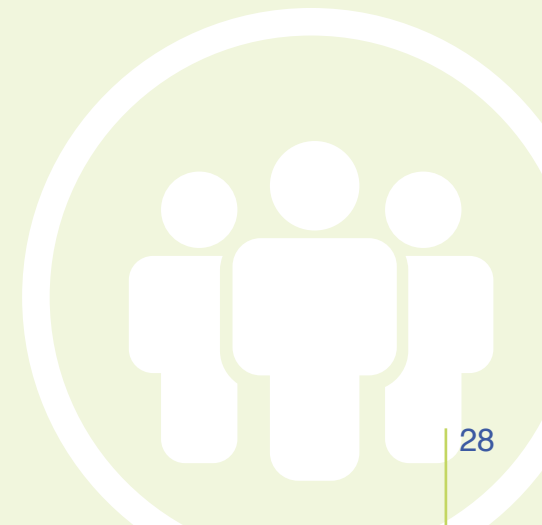
(Schwartz et al., 2020). Furthermore, financial access differed relative to the type of tick-borne disease and attitudes toward preventative practices. High-income areas with low crime rates, homelessness rates, and housing vacancies were associated with lower incidence of ehrlichiosis and Lyme disease (Springer & Johnson, 2018). People with high incomes reported increased willingness to apply pesticidal treatments to their property and utilize tick preventatives for pets (Niesobecki et al., 2022).

The scoping review identified several publications that explored differences in age, race, and geographic region and access to care. However, there were gaps in the literature. Few studies investigated tick-borne diseases as they relate to race or ethnicity. Most studies of disparities among minority groups focused on Hispanic groups; however, Hispanics groups are underrepresented in surveys and long-term surveillance studies (Brummitt et al., 2020; Kuriakose et al., 2020). However, surveys of Hispanic populations designed to measure knowledge of ticks, tick-borne diseases, and attitudes toward preventative measures determined that, although as likely as non-Hispanic White individuals to utilize protective measures, Hispanic individuals are less likely to perform tick checks, identify ticks as vectors of disease, and identify signs and symptoms associated with Lyme disease (Beck et al., 2021; Hu et al., 2019). Furthermore, lower rates of using protective measures and less knowledge of ticks and tick-borne diseases were associated with primary language (Hu et al., 2019). Primary Spanish speakers were less likely to identify ticks as vectors for Lyme disease or identify symptoms of Lyme disease than were primary English speakers after adjusting for education, ethnicity, and other factors (Hu et al., 2019). Future research should embed equity into study design to gain an accurate measure of high-risk and at-risk groups.

Discussion: Scoping Review Results and Limitations

The objective of the literature review was to comprehensively characterize tick-borne disease research since 2018 within broad but specified parameters. Results presented in this chapter characterize the volume of publications and the trajectory of research on tick-borne diseases and associated illnesses from January 1, 2018, to June 30, 2022. The inclusion and exclusion criteria presented in Table 2 were carefully considered and refined throughout the scoping review process to capture as much literature as possible while ensuring completion of the review. However, one limitation is the potential that original literature was missed while scoping the literature.

The body of literature for tick-borne diseases and associated illnesses is incomplete yet vast. Results show increasing numbers of both published and unpublished literature since 2018. The largest number of articles related to tick-borne diseases and associated illnesses were published in 2021, and it appears likely that the number of publications in 2022 will outpace 2021. Following the set parameters, publications were then categorized according to 2022 Tick-Borne Disease subcommittee themes to provide an alternative analysis of the literature. The weight of the literature heavily favors diagnosis and disease

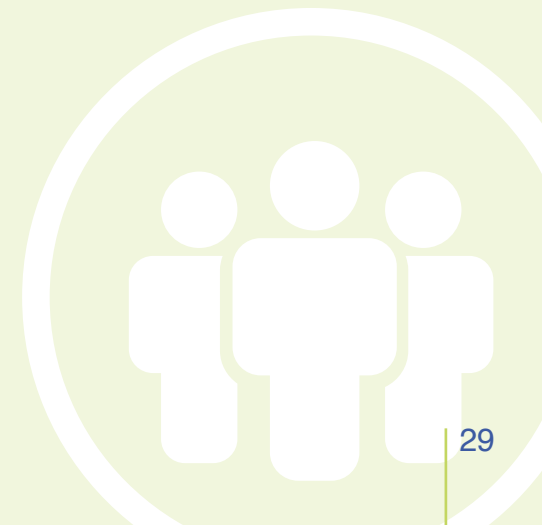


surveillance. Publications discussing pathogenesis, clinical presentation, and treatment of tick-borne diseases and associated illnesses accounted for less than 10% of the published literature. Of note, Lyme disease accounted for most publications overall and in each year. Nearly 75% of published articles were case studies or publications reporting on surveys including disease surveillance and monitoring programs, disease prevalence surveys, education surveys on tick-borne diseases and associated illnesses, and tick surveillance. A catalogue of all published articles can be found in Appendix F.

Specific topics of significance such as access to care, clinician education, equity, impact of climate change, specific emerging tick-borne diseases such as AGS, and tick biology require devoted literature reviews that were beyond the scope of this review. It should be noted that the literature discussed herein are publications that met the defined inclusion criteria and some original literature may have been missed.

Due to time constraints, analyzing and annotating all identified literature was beyond the scope of this review. Instead, the report describes annotated grey literature to highlight certain novel and emerging research. However, the unpublished literature should be reviewed with caution because the publications were not peer-reviewed and did not undergo formal quality assessment. In addition, clinical trial information is often limited; for example, if the course or progress of a clinical trial is altered, notification of this change is not always reported in a timely manner, and study success remains undetermined.

The literature discussed in this chapter mapped ongoing progress and discussed noticeable gaps. The need for public and clinician education regarding the risks of tick-borne diseases continues, even among individuals who are aware of the risks. Unpublished research demonstrated potential methods to provide education to health care professionals (Blanken-Little, 2021). The ongoing development of tick-borne diseases vaccines provides promising potential, especially for a vaccination against Lyme disease. Prevention measures beyond vaccines require additional research, but the refining of known methods and efforts to develop new methods to control tick populations continues.



Chapter 4: Surveys

Introduction

As reported above, a federal inventory of tick-borne diseases related to funding, activities, and programs at the federal agency level was conducted in 2018 and 2020. To build on and augment previous efforts of the Working Group, the 2022 inventory was expanded to become the Tick-Borne Disease National Inventory, which includes a revised federal agency survey and newly added state and private organizations survey components. Through detailed surveys, data were collected and analyzed to gain a greater understanding of tick-borne disease funding, research, surveillance, education, outreach, and access to care in the United States. Specifically, the goal was to assess activities that receive the greatest focus and to identify gaps related to issues prioritized by the 2022 Working Group and its subcommittees. In addition, the survey design lays the groundwork for future tick-borne disease national inventory activities. This chapter presents the survey results as well as relevant additional information.

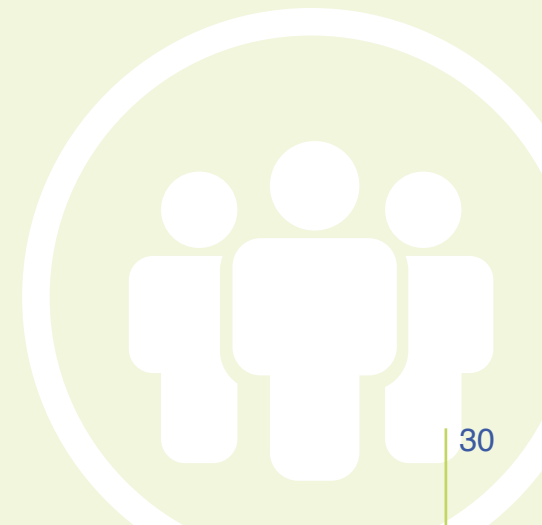
Methods for All Surveys

The survey for the national inventory was created by adapting the Tick-Borne Disease Working Group Federal Inventory surveys used in 2018 and 2020. Additional survey questions were derived from the priority findings of the 2022 Working Group subcommittee reports (Tick-Borne Disease Working Group, 2022), which outlined pressing areas of need within the tick-borne disease landscape. The goal was to ensure that the surveys collected data salient to the efforts of the 2022 Working Group, thus enabling the identification of gaps in tick-borne disease funding, programs, and activities. The survey was then tailored specifically for each survey group, that is, federal agencies, states, and private organizations. Survey questions were both open and closed to yield quantifiable results and enable analysis while providing the flexibility needed to collect information regarding programs that could not be captured in the closed survey format.

Described in greater detail below, the entire survey process—from April to September 2022—consisted of a series of steps involving advice, survey development, feedback, and survey refinement with participation from multiple stakeholders and subject matter experts.

Survey Development

A federal inventory group was formed to advise the survey process. Over a 6-month period, regular briefings were held with the advisory group to provide status updates and seek input and feedback when needed. This group consisted of several Working Group members, representatives from federal



agencies, and OIDP and OASH staff members who advised on, for example, which organizations to survey, survey content, and survey drafts; offered additional information (e.g., state data reported to CDC); identified appropriate points of contact to complete the questionnaires; and facilitated survey dissemination and collection.

Survey Dissemination

The questionnaires were created and distributed using SurveyMonkey, an online survey tool that enables the collection of data in Excel spreadsheets, thus facilitating analysis. Survey recipients were given 1 month to complete the questionnaires with the possibility of an extension if requested. All recipients received reminder emails to encourage participation. Respondents were contacted when clarification of information reported was required.

Survey Analysis

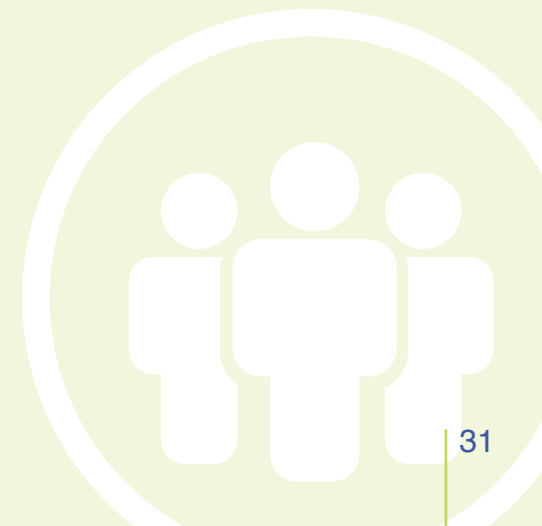
Survey response data were exported into Microsoft Excel spreadsheets. For each question, the data were coded and converted into descriptive statistics such as percentages and frequencies. Responses to open-ended questions, such as “other,” were summarized and included in the text of the results.

To determine the respondents’ focus areas, data were separated into two categories: research and programs and activities. Special attention was paid to priority issues identified in the 2022 Working Group subcommittee reports, including health equity, streamlined commercialization of tick bite prevention and control products as well as innovative diagnostic technologies, and tick-borne diseases education. These decisions guided the analysis and development of graphs.

Other sources were used to supplement survey responses, such as state reports identified via the scoping review, the National Association of City and County Health Officials’ (NACCHO) 2020 Vector Control Assessment (NACCHO, 2020), additional information submitted by respondents, and agency and private organization websites. Information gathered from these sources is included in the text of the results.

Findings: Federal Agency Surveys

The Working Group conducted surveys of federal agencies in 2018 and 2020. Several questions from the earlier survey were included in the 2022 federal agency survey, and additional questions were added regarding funding, staffing, programs and activities, research, and plans related to tick-borne diseases. Agencies were selected based on their participation in surveys during the 2018 and 2020 cycles and were as follows.



- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare & Medicaid Services (CMS)
- National Institutes of Health (NIH)
- U.S. Department of Agriculture (USDA)
- U.S. Department of Defense (DoD)
- U.S. Department of Veterans Affairs (VA)
- U.S. Food and Drug Administration (FDA)

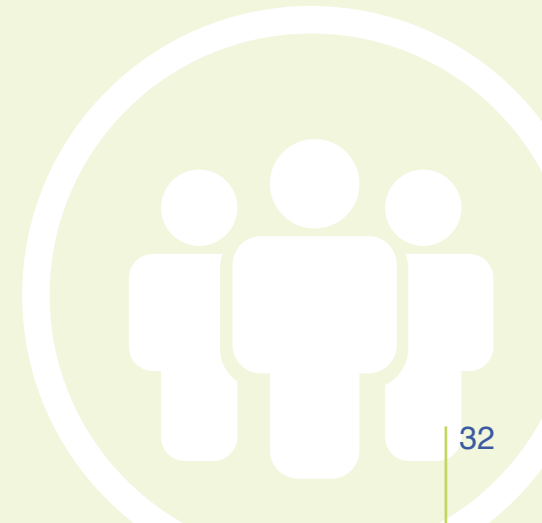
Methods

A memo requesting survey participation were sent from the Office of the Assistant Secretary of Health, ADM Rachel Levine, to each federal agency. The memo outlined the objectives of the survey and included a link for participation. Agencies were given 4 weeks to participate with an allowance for extension on request if necessary. Reminder emails were sent prior to the deadline to ensure optimal participation rates, which resulted in a 71% participation rate (5 out of 7 agencies). CMS data are not included in the results, which is explained in the federal agency section in Chapter 4. VA did not respond to the survey. The results from the participating federal agencies are reported below.

Two federal agencies (i.e., USDA and DoD) had multiple divisions and departments that conduct tick-borne disease activities, programs, and research. In some cases, these divisions and departments supplied the information separately. For data analysis purposes, their responses were combined to become a single agency answer where appropriate. When specific division or department information is reported it is noted.

Funding

Four federal agencies disclosed their funding levels for tick-borne diseases from FY2018 to FY2021 (Figure 7). FDA reported no dedicated funding for tick-borne diseases during that period.



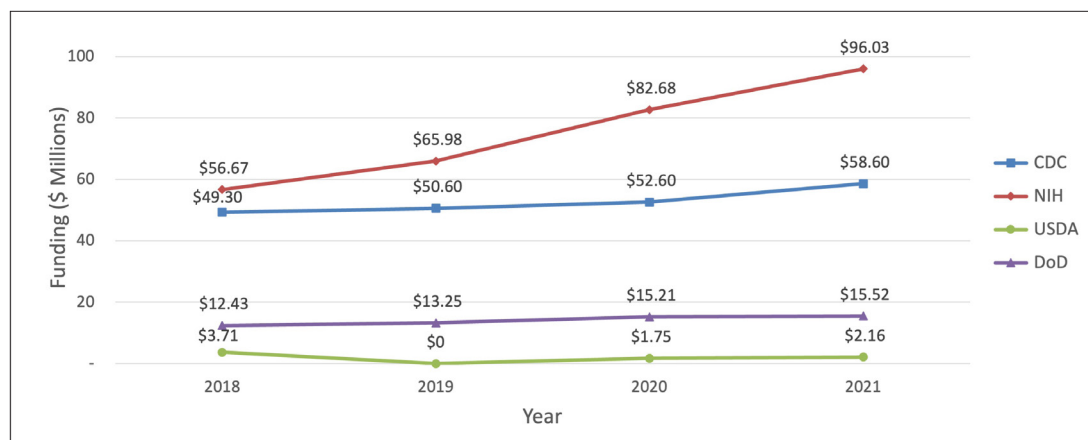


Figure 7. Funding for tick-borne disease activity by federal agency, FY2018–FY2021.

NIH reported the highest funding for tick-borne disease activities. CDC and DoD funding have increased, while USDA’s funding has declined. Notably, however, USDA does not conduct its own programs or activities related to ticks and tick-borne diseases; instead, the agency funds external research.

Staffing

Agencies reported numbers of full-time and support staff engaged in tick-borne disease activities (Table 3). The number of employees were recorded as 0, 1–9, 10–19, 20–49, and 50+. The survey separated full-time employees into two categories: full-time employees supported by dedicated tick-borne disease funds and full-time employees dedicated to tick-borne disease activities (e.g., an employee performing such activities but whose position is not supported by a dedicated source of tick-borne disease funding).

Table 3. Federal Agency Staffing Related to Tick-Borne Diseases and Associated Illnesses.

	Full-Time Employees	Support Staff
CDC	>50	>50
DoD	<10	<20
FDA	<10	0
NIH	<20	<50
USDA	<20	<50

CDC has the most staff dedicated to tick-borne disease activities of any agency, with more than 50

FDA reported no dedicated funding for tick-borne diseases for FY2018 through 2021.



full-time employees and support staff. This number reflects an increase from the fewer than 35 full-time equivalent positions dedicated to tick-borne disease activities reported in the 2018 and 2020 inventories.

Programs and Activities

All participating agencies were provided a list of program and activity types and asked to “indicate whether each category was relevant to agency programs or activities involving tick-borne diseases and conditions.” Results are illustrated in Figure 8.

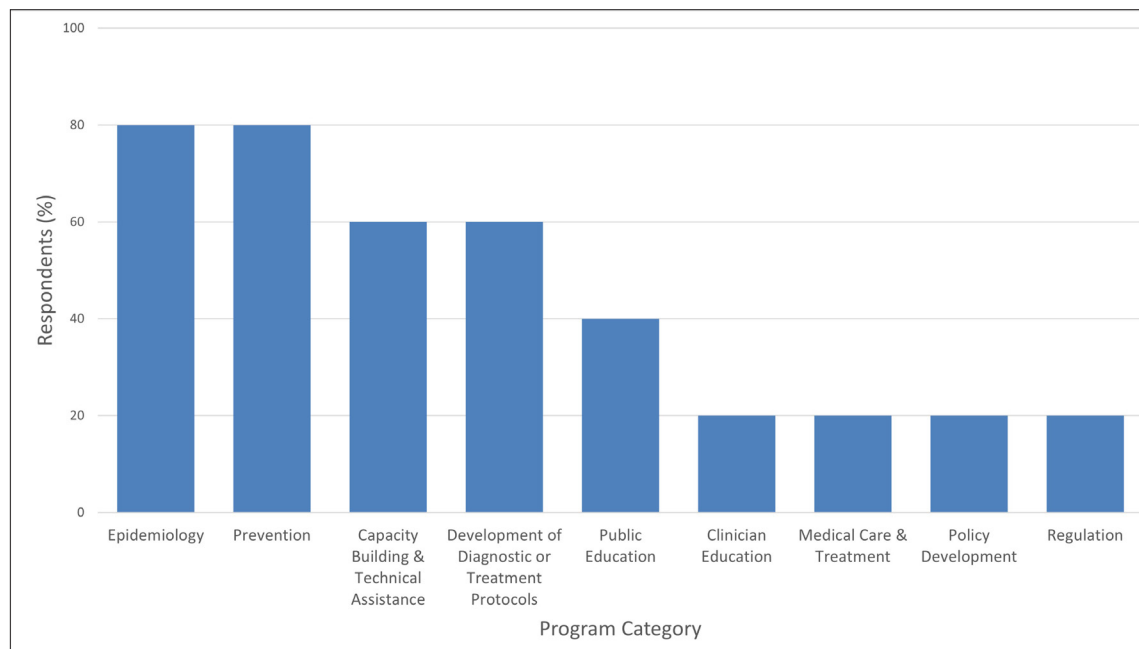


Figure 8. Programs and activities funded or conducted by federal agencies.

CDC, DoD, NIH, and USDA reported programs and activities related to epidemiology and prevention (80%). CDC, DoD, and USDA reported activities related to capacity building and technical assistance (60%). CDC, NIH, and USDA fund or conduct the development of diagnostic or treatment protocols (60%). All agencies reported engaging in activities to increase adoption of tick bite prevention or control methods (100%); yet, efforts to educate the public or health care providers are inadequate.

No agencies reported having programs related to medical care and treatment, mental health services, or support groups.



Only NIH reported funding or conducting medical care and treatment programs, while only CDC indicated work related to policy development. FDA reported funding or conducting programs in regulation. No agency reported programs or activities related to mental health services, support groups, or other supportive services.

To better understand federal efforts as they relate to the major themes of the Working Group, respondents were also asked to indicate whether they funded or conducted programs related to the 2022 Working Group subcommittee topic areas. The results are illustrated in Figure 9.

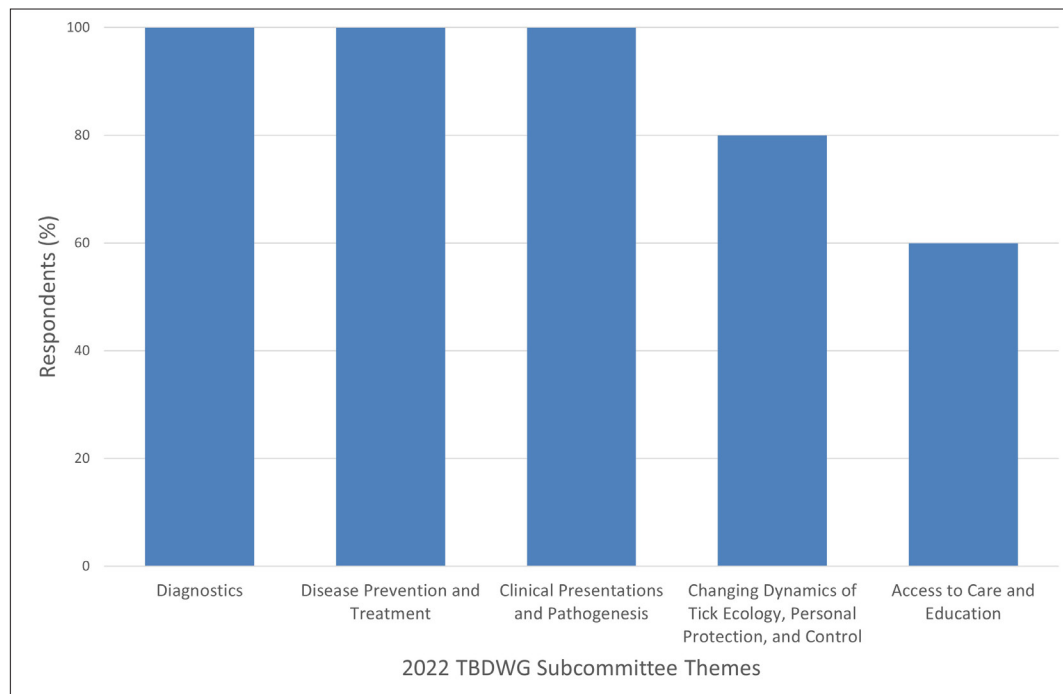


Figure 9. Programs, activities, or research relating to Working Group subcommittee themes supported by federal agencies.

CDC, FDA, and NIH reported projects related to access to care and education (60%). CDC develops training modules for health care providers about preventing, diagnosing, and treating tick-borne diseases and associated illnesses that include material on the mental health aspects of Lyme disease, race, and characteristic-based tick-borne disease presentations, educating patients with AGS on avoidance measures, and the impact of bartonellosis on high-risk patients (20%).

CDC and USDA are the only two agencies with projects related to public education (40%).

CDC alone reported activities related to clinician education programs.



All agencies reported efforts in clinical presentations and pathogenesis. Specifically, agencies focused on understanding the mechanisms of pathogenesis including autoimmunity, latency, persistence, and reemergence via central nervous system infection (60%), persistent symptoms (80%), allergy (60%), immunity (80%), autoimmunity (60%), and pregnancy (40%).

Moreover, CDC and DoD fund or conduct research related to the impact or mechanisms associated with tick-borne disease and pregnancy (40%). DoD and NIH fund or conduct longitudinal research to determine the mechanisms of pathogenesis of post-treatment Lyme disease and to define the burden and extent of persistent symptoms (40%).

In addition, all agencies indicated funding or conducting projects related to diagnostics (100%). These efforts included the following:

- Promoting the evaluation and development of current and promising new diagnostic approaches (100%) through research grants and funding opportunities, and funding research aimed at identifying host immune markers that may facilitate diagnosis (80%)
- Minimizing roadblocks and streamlining the process for getting new tick-borne disease diagnostics to market via funding research related to tick-borne disease diagnostic development and/or early commercialization (80%); and developing testing methodologies that detect different types and stages of Lyme disease (other than acute) or other elusive tick-borne infections (60%)

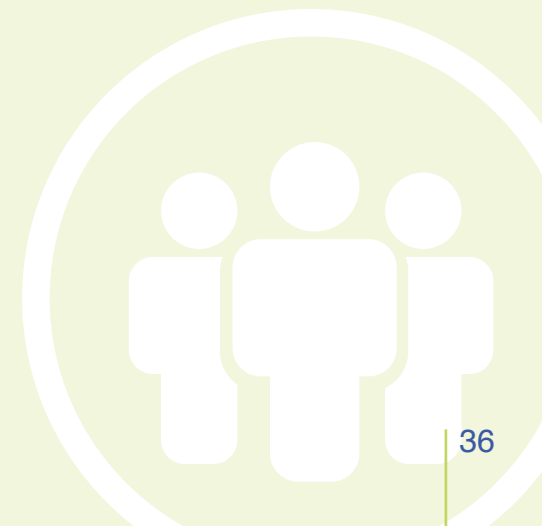
No agencies reported work to identify or implement solutions that streamline the regulatory pathway for getting new tick-borne disease diagnostic offerings to market.

Agencies were asked to indicate whether they fund any biorepositories of human tick-borne disease samples. CDC funds a Lyme disease serum repository, and CDC and NIH co-fund a biorepository of human tick-borne disease samples. In addition, NIH allows external researchers access to samples at no cost.

However, federal efforts were limited regarding the education of policymakers, reviewers, researchers, and clinicians on the unique challenges of diagnostic test development and the commercialization pipeline for tick-borne disease diagnostics. CDC and NIH conduct activities to educate researchers, doctors, and advocates on the latest science, working hypotheses, and future research needs (20%) and on longitudinal research to determine the long-term effects of tick-borne diseases and treatment efficacy (20%). The survey results also revealed that no federal agencies are funding outreach programs on the benefits of participating in clinical studies for tick-borne diseases.

All five agencies reported activities related to disease presentation and pathogenesis. Efforts included funding research to better understand coinfections (80%), clinical manifestations (60%), and the magnitude and outcomes of vertical transmission (60%).

No agency reported research related to health equity for patients with tick-borne illnesses, such as assessing disparities and their root causes or evaluating research methods for blind spots.



DoD, USDA, and NIH engage in prevention research in several areas: vaccine research (60%), such as putative vaccine antigens (60%), cross-protective potential of existing tick-borne encephalitis vaccine (40%), vaccines and immunotherapeutics that include the use of next-gen platforms (60%), novel methods for blood screening (40%), and pathogen inactivation for tick-borne disease pathogens (40%).

However, limited work on disease treatment is being performed, with only 40% of agencies reporting research efforts to develop antimicrobial compounds and antibody therapies for acute or persistent tick-borne infections, causes of persistent symptoms attributed to tick-borne diseases, and development of therapeutic approaches for persistent symptoms.

CDC, DoD, NIH, and USDA reported funding or conducting programs related to tick ecology, personal protection, and control (80%), as follows.

- Minimizing roadblocks for getting new tick bite prevention and tick control products to market, including funding programs that facilitate the commercialization of tick-borne disease intervention products to market (60%) and that test the effectiveness of new or existing tick bite prevention products or interventions (80%)
- Defining the primary drivers of tick populations, tick pathogen prevalence, and geographic expansion of ticks and tick-associated diseases (80%), including rapid identification of tick species and discovery of the pathogens they transmit (80%), and expanding knowledge and increasing adoption of tick bite prevention or tick control methods (60%)

The Access to Care and Education Subcommittee (2022) developed two recommendations regarding Lyme disease training and educational modules with the rationale that “well-informed clinicians are critical to reducing the burden of [tick-borne diseases].” Respondents were asked to describe any clinician-oriented educational activities. CDC, DoD, NIH, and USDA reported funding or engaging in activities to educate and increase adoption of tick-borne disease prevention or control methods through multiple means, such as publishing technical guides for service members (DoD’s Armed Forces Pest Management Board) or medical surveillance monthly reports (CDC). A list of educational activities and the number of participating agencies is provided in Table 4.

NIH was the only agency to report funding research aimed at improving treatment and management options for Alpha-gal Syndrome.

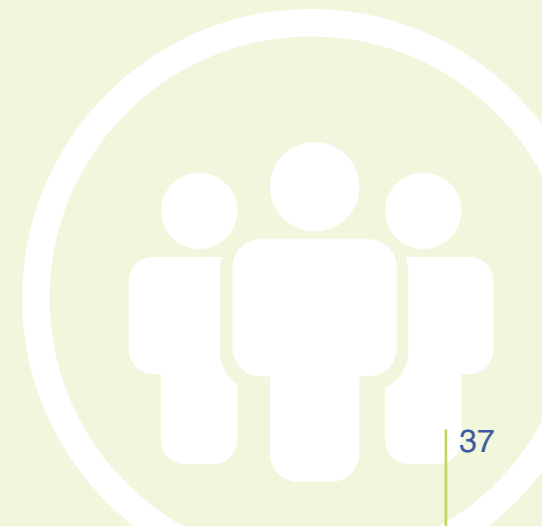


Table 4: Educational Activities Supported by Federal Agencies

Categories	Respondents (n)
Educate and Increase Adoption of Tick-Borne Disease Prevention or Tick Control Methods	4
Educate Researchers, Doctors, or Disease Advocates on the State of Science	2
Develop Training Modules for Providers on Lyme Disease	1
Develop Training Modules for Providers on Diseases other than Lyme disease	1

CDC and NIH were the sole agencies to report educating researchers, doctors, or disease advocates on the latest science, working hypotheses, or future research needs. Both agencies also provide web-based content to educate health care providers about preventing, treating, and diagnosing tick-borne diseases. Content includes mental health aspects of Lyme disease; educating patients with AGS regarding avoidance measures; bartonellosis and its impact on high-risk patients (e.g., people experiencing homelessness or those who are immunocompromised); and race or characteristic-based disease presentations.

In the category of diagnostics, CDC, DoD, and NIH develop testing methodologies to detect different types and stages of Lyme disease. For example, DoD reported funding research to identify the underlying mechanisms of persistent neurological symptoms associated with post-treatment Lyme disease, while CDC is funding a program to develop serological assays for increased sensitivity and specificity of early Lyme disease.

Future Plans

Federal agencies were asked to indicate their plans to increase funding related to tick-borne diseases and associated illnesses in the following areas:

- Pathogenesis (NIH)
- Treatment (NIH)
- Public education (NIH)
- Clinician education (CDC)
- Diagnostics (CDC, FDA, NIH)

No federal agencies reported funding or conducting programs related to product development.

- Clinical presentation (FDA, NIH)
- Disease prevention (FDA, NIH)
- Employer education (CDC, FDA)
- Personal protection (CDC, NIH)
- Access to care (CDC, FDA, NIH)
- Changing Dynamics of Tick Ecology (CDC, DoD, FDA, NIH)

In the category of “Other,” agencies identified tick-ecosystem interaction (DoD), peer-review (NIH) and meritorious research (NIH) as additional areas where they plan to increase tick-borne disease funding.

CMS Pilot Feasibility Study

Responses from CMS were not included in the previous two federal inventories conducted by the Working Group. CMS was not a participant in the 2018 inventory, and the survey tool for the 2020 inventory was not tailored to the unique activities of CMS. As a result, in its 2020 Report to Congress, the Working Group made the following recommendation:

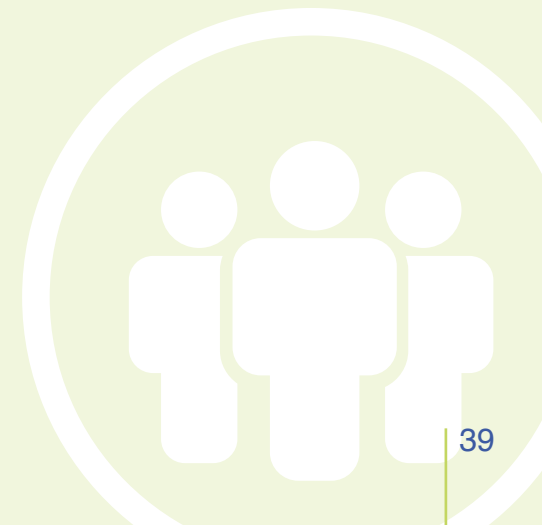
Recommend that CMS provides all information and data on Lyme disease and other tick-borne diseases and all applicable agency activities pertaining to these conditions which may include but should not be limited to:

- 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. (Tick-Borne Disease Working Group, 2020)

Because previous attempts to collect CMS data had been unsuccessful, and given the restrictive timeline for data collection, the plan for this national inventory proposed adaptation of an existing, or development of a new, data collection framework for CMS that better reflects the agency’s activities and addresses this recommendation. In consultation with the inventory advisory group and CMS representatives, it was determined that a pilot feasibility of CMS Medicare reimbursement data for FY2018 would yield the desired information. Follow-up consultations were held with CDC scientists and epidemiologists to discuss the construction of a framework using a similar methodology from a previous study conducted by CDC measuring CMS Medicare reimbursement data (Schwartz et al., 2021).

Included in the framework is a request for Medicare data related to tick-borne disease International Classification of Diseases (ICD)-9 and ICD-10 diagnostic codes, common treatments and related symptoms, demographic information, and reimbursement costs for FY2018. The intent was to develop,

CDC, NIH, DoD, and FDA plan to increase staffing to support tick-borne disease programming, activities, and research.



collect, and analyze data to assess the framework's feasibility while also informing this report; however, the effort was hindered by time constraints and was not achieved. It is hoped that the framework developed for the CMS pilot feasibility study can be used in subsequent inventories or as a stand-alone initiative to collect CMS Medicare data to inform on reimbursement costs of tick-borne diseases in the future.

Findings: State Surveys

The survey of states was an additional component in this cycle of the national inventory. The survey was specifically tailored to collect data from states regarding funding, staffing, and programs related to tick-borne diseases and associated conditions. Due to the Paperwork Reduction Act (44 U.S.C. § 3501) and time limits, data collection was restricted to surveying nine states. In consultation with the inventory advisory group and CDC, the following states with the highest incidence of tick-borne diseases that provide funding for or conduct tick-borne disease research and activities were identified for survey participation.

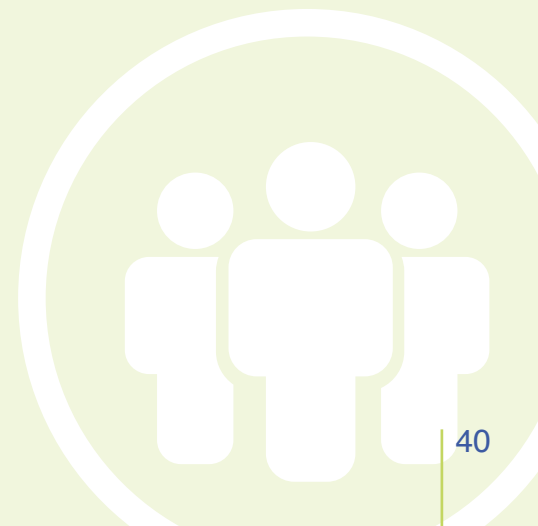
Connecticut	New Jersey	Vermont
Indiana	New York	West Virginia
Maine	Pennsylvania	Wisconsin

Five out of the nine states responded to the online survey: Maine, New Jersey, New York, Pennsylvania, and West Virginia, resulting in a 56% participation rate. Connecticut, Indiana, Vermont, and Wisconsin declined participation.

To augment state information, additional sources of state data were collected and included in this report. State and local surveillance and control data reported by NACCHO in the 2020 Vector Control Assessment are also included (NACCHO, 2020). In addition, the scoping review process yielded the retrieval of annual state reports from an additional 10 states. The results of the surveys and supplemental information are reported below.

Methods

Points of contacts for each state were identified through consultation with the inventory advisory group. These individuals were invited to participate via an email that explained the objectives and timelines related to participation. Survey links were emailed to state contacts on June 3 and 4, 2022, with a request to respond within 4 weeks and allowance for extensions if necessary. Reminder emails were sent 1 week prior to the deadline to ensure optimal participation rates.



Funding

Four states—New Jersey, New York, Pennsylvania, and West Virginia—disclosed their tick-borne disease funding levels for FY2018 through FY2021 (Figure 10). No clear trend in funding levels across reporting states can be stated. New Jersey, Pennsylvania, and West Virginia reported increases in funding for tick-borne diseases, and New York reported a sharp decrease.

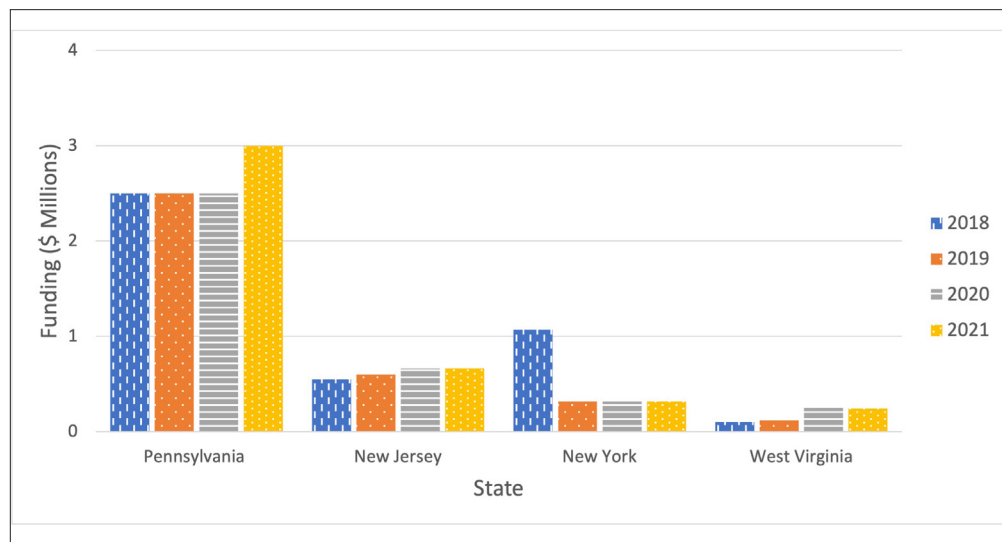


Figure 10. State funding for tick-borne diseases, FY2018–FY2021.

States were asked whether they “participate or fund any private-sector partnerships to address tick-borne diseases” to determine partnership activity within their states. New Jersey, New York, and Pennsylvania indicated funding academic institutions to conduct tick-borne disease research. Maine, New Jersey, and New York reported funding private-sector partnerships in areas such as diagnostics, education, disease prevention, personal protection, and tick ecology.

Staffing

States were asked to indicate their staffing levels dedicated to tick-borne diseases. The staffing categories are the same for each survey group (categories of (0, 1–9, 10–19, 20–49, and 50+). Results are reported in Table 5. All respondents reported employing dedicated full-time staff supported with tick-borne disease funds.

Pennsylvania’s state legislature and Governor prioritized funding for Lyme disease in 2018.



Table 5. State Staffing Related to Tick-Borne Diseases and Associated Illnesses.

	Full Time Employees	Support Staff
Maine	<20	0
New Jersey	<20	<10
New York	<10	<10
Pennsylvania	<10	0
West Virginia	<10	0

Programs and Activities

States were asked to report tick-borne disease programs or activities either funded directly by the state or indirectly by the federal government, by category. All states respondents reported conducting programs or activities in public education, clinician education, epidemiology, and prevention. In addition, states reported programs or activities in the following areas:

- Capacity building and technical assistance (Maine, New Jersey, New York, West Virginia)
- Policy development programs (Maine, New Jersey, and New York)
- Development of diagnostic or treatment protocol programs and regulation (New Jersey, New York)
- Medical care and treatment (New York)

As with the federal agencies, no states indicated programs related to mental health services, support groups, or other patient support services.

The survey asked the states to identify which tick-borne diseases or associated illnesses are addressed by these by state programs or activities. All states reported programs that address anaplasmosis, babesiosis, Lyme disease, spotted fever group rickettsioses (including RMSF), and coinfections. Maine, New Jersey, and New York reported programs that address tick-borne relapsing fever, Bourbon virus, and Heartland virus. Maine, New Jersey, and Pennsylvania have programs that address AGS.

Figure 11 shows the percentage of state respondents that are funding or conducting programs that align with the 2022 Working Group subcommittee themes. The following sections provide further detail about the work reported in each thematic area.

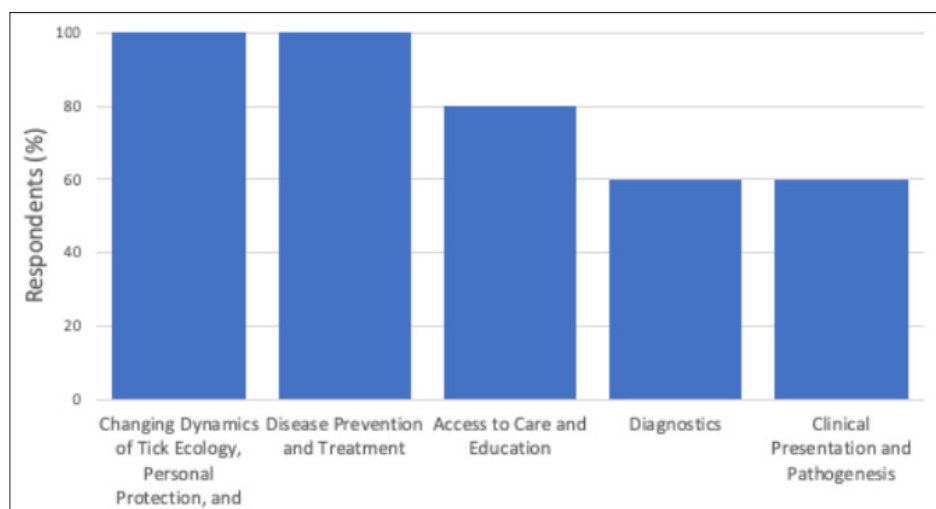


Figure 11. States funding or conducting programs related to the 2022 Working Group subcommittee themes.

Changing Dynamics of Tick Ecology, Personal Protection, and Control

All states indicated programs or activities related to changing dynamics of tick ecology, personal protection, and control. Within this category, states are primarily funding or conducting activities related to

- administering local public health management programs aimed at tick bite prevention and tick control (100%) and investigating the effectiveness of new or existing tick control products or interventions (60%);
- defining the primary drivers of tick populations, prevalence, and geographic expansion of ticks and tick-associated diseases, including rapid identification of tick species and discovery of the pathogens they transmit (80%) and data collection on current or forecasted tick distribution (100%); and
- expanding knowledge and increasing adoption of tick bite prevention and tick control methods, including activities to increase adoption of tick bite prevention and tick control methods (100%) and to overcome the public's limited use of tick bite prevention methods and tick control methods (80%).

All five states reported conducting vector surveillance for tick-borne diseases.

Four states conduct local or regional surveillance and reporting of tick-borne diseases.



Tick Surveillance

All five states report conducting vector surveillance, but only New York and West Virginia share these data with the public. Four states (New Jersey, New York, Pennsylvania, and West Virginia) provide rapid identification of tick species and discovery of the pathogens they transmit through various means, such as active surveillance, pathogen testing of ticks, and DNA barcoding of ticks.

Disease Prevention and Treatment

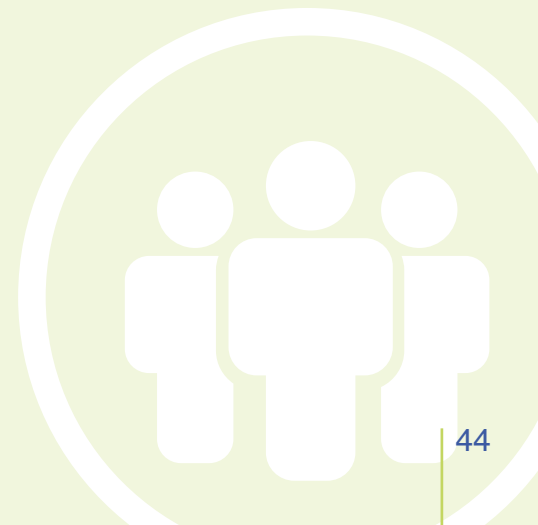
All states reported at least some activity related to disease prevention and treatment. State efforts in this area primarily center on educating policymakers, reviewers, researchers, and clinicians on the unique challenges of diagnostic test development and the commercialization pipeline for tick-borne disease diagnostics through online training modules and websites (80%). However, New York also conducts longitudinal research to address the long-term effects of tick-borne disease or to determine treatment efficacy (20%). Four states (80%) reported conducting local or regional surveillance and reporting of tick-borne diseases and associated illnesses.

Access to Care and Education

Four states—Maine, New Jersey, New York, and Pennsylvania—reported activities related to access to care and education (80%). All states indicated activities relevant to accessing care, that is, ensuring health equity for patients with tick-borne diseases. These activities include

- ensuring access to telehealth (100%);
- offering training modules or website content for clinicians and other health care providers concerning preventing, diagnosing, and treating Lyme disease (60%). Only New Jersey and Pennsylvania include information on race- or characteristic-based information in presentations of Lyme disease; and
- offering training modules or website content for clinicians and other health care providers concerning preventing, diagnosing, and treating tick-borne diseases other than Lyme disease (80%). Only New Jersey includes race- or characteristic-based information in tick-borne disease presentations. No states provide information on the impact of these diseases or conditions on high-risk populations, such as individuals experiencing housing insecurity or immunocompromised patients.

Maine, New Jersey, New York, and Pennsylvania educate researchers, health care providers, and advocates on new research findings, working hypotheses, and research gaps through educational outreach activities, webinars, question and answer documents, and health alert messaging. New Jersey was the only state to report providing public education on the benefits of participating in clinical studies.



Maine, New Jersey, New York, and Pennsylvania offer annual training modules or website content for health care providers about preventing, diagnosing, and treating Lyme disease. However, none of these states reported including the mental health aspects of Lyme disease in its offerings. New Jersey, New York, Pennsylvania, and West Virginia offer modules on tick-borne diseases and illnesses other than Lyme disease. This content is posted to the state department of health websites, but updates of these websites vary from state to state. No information is provided by any state on bartonellosis and its impact on high-risk patients, such as individuals experiencing housing insecurity or immunosuppressed and/or immunocompromised patients.

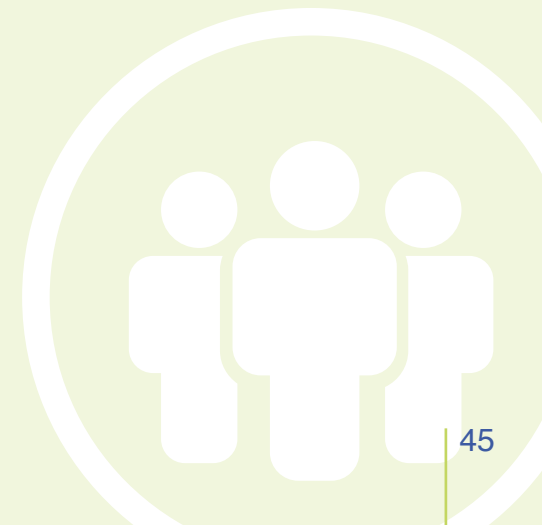
Clinical Presentation and Pathogenesis

Three states (New Jersey, New York, and West Virginia) reported activities in the areas of clinical presentation and pathogenesis (60%). However, these states are doing limited work to understand the mechanisms of pathogenesis including autoimmunity, latency, persistence, and reemergence specifically. New York is the only state to report conducting research on the mechanisms of tick-borne disease pathogenesis (e.g., central nervous system infection, persistent symptoms, immunity, and autoimmunity). New York and Pennsylvania are conducting tick-borne disease research that includes a representative cross-section of patients from a variety of geographic, racial, ethnic, and socioeconomic backgrounds.

No states reported efforts to address neuropsychiatric Lyme disease and mental health issues associated with tick-associated illnesses or to investigate the prevalence of undetected tick-borne diseases among subgroups of the population that may have high burden of multi-systemic chronic conditions (e.g., individuals in prisons, homeless shelters, etc.).

Health Equity

The state survey included questions related to high-risk populations to gain a deeper understanding of work at the state level to address health equity issues of tick-borne diseases and associated illnesses. As shown in Figure 12, states primarily target children as a sub-group in their programmatic efforts, with programs aimed at tick bite prevention and control (80%). These programs include but are not limited to public service announcements (e.g., posters, pamphlets), K-12 curricula, training for local health educators and human and veterinary medical professionals, and tick prevention signage on state public lands. Only New Jersey (20%) reported providing guidance on these topics in languages other than English.



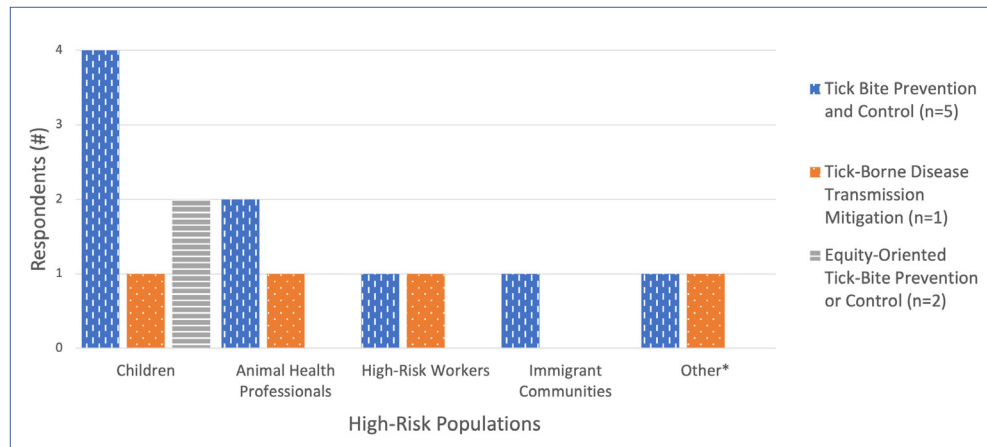


Figure 12. Programs focused on high-risk populations conducted or funded by states. *Other: Forestry workers.

Bringing Products to Market: Tick Bite Prevention, Tick Control, and Diagnostics

States were queried about their efforts to bring new products to market (Figure 13). Findings revealed limited work at the state level. Maine, New Jersey, and New York reported efforts in diagnostics (60%). New Jersey and New York are promoting the evaluation of current diagnostic approaches and development of new diagnostic approaches. In fact, New York has successfully developed and validated a diagnostic assay for Heartland virus and is working on similar assays for Bourbon virus and Dabie vandavirus.

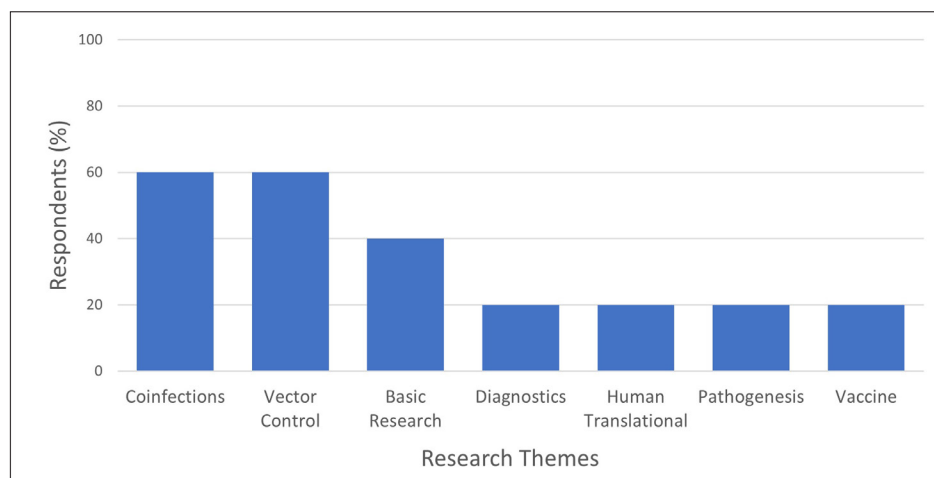


Figure 13. Research efforts by states.

No state reported activities focused on communities of lower socioeconomic status, pregnant people, or Indigenous communities.



Research

States reported limited research efforts compared to private organizations and federal agencies. New Jersey, New York, Pennsylvania, and West Virginia are conducting research that investigates the drivers of tick populations, tick pathogen prevalence, and/or geographic expansion of ticks and tick-associated diseases. New Jersey attempted to conduct research that investigates the effectiveness of existing tick bite prevention strategies or products; however, its efforts resulted in a non-research determination. No other states reported research in this area. New York is the only state to report research aimed at developing promising new diagnostic technologies in tick-borne diseases, identifying host immune markers to facilitate diagnosis, and developing putative vaccines.

Future Plans

Survey respondents were asked to indicate their plans to expand funding in terms of research and policy development, including cross-sector collaborations. Three of five states have no plans to expand tick-borne disease funding, research, or initiatives. Other states' plans for future expansion are as follows:

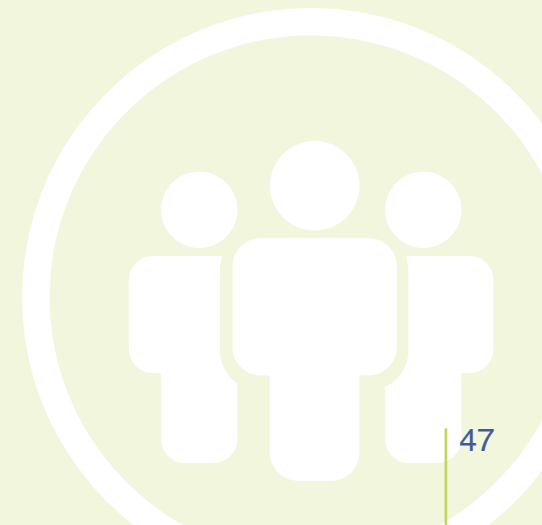
- Education, general (New Jersey, Pennsylvania, West Virginia)
- Clinician education (Pennsylvania, West Virginia)
- Personal protection (Pennsylvania)
- Diagnostics (New York)
- Public education (Pennsylvania)
- Employer education (Pennsylvania)
- Disease prevention (Pennsylvania)

Notably, no states reported plans to expand funding for tick ecology, access to care, service members, veterans, and their families, treatment, clinical presentation, and pathogenesis. However, New York and West Virginia indicated plans to increase staffing to support tick-borne disease programming, activities, and research. In addition, New Jersey, New York, and West Virginia intend to expand cross-sector collaborations for tick-borne disease activities. For example, West Virginia seeks to collaborate with neighboring state health departments.

State Reports

Several U.S. states publish public health reports, often annually, with information about human and tick surveillance efforts and other tick-borne disease activities within the state. The unpublished literature search yielded 42 such reports, from which 10 additional states were identified that had not participated

No state has identified or implemented solutions that streamline the regulatory pathway to move new tick-borne disease diagnostic products to market.



in the survey. Therefore, to supplement survey results, the most recently published state reports were used to draw data related to programs and activities regarding tick-borne disease activities. A synthesis of the data collected from the following states is provided in Figures 14 and 15. Reports reviewed included information from the following states:

California	North Carolina
Maine	North Dakota
Massachusetts	Oregon
Minnesota	Ohio
New Hampshire	Vermont

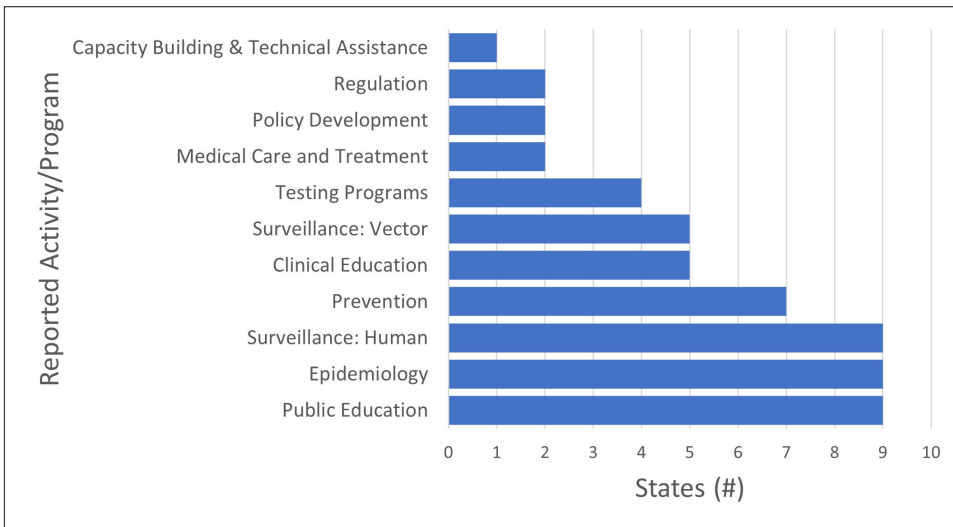
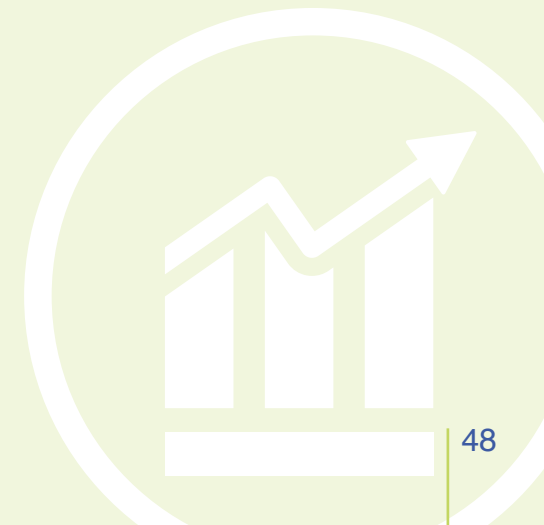


Figure 14. State-supported tick-borne disease activities and programs, FY2018–FY2022.

It should be noted that states often conduct more programs, activities, and research than are presented in annual reports. For a comparable and comprehensive accounting between states, a more in-depth evaluation would be required.

West Virginia hopes to make Alpha-gal Syndrome a reportable illness in the state.

Nine out of 10 states reported activities or programs in areas of surveillance, epidemiology, and public education.



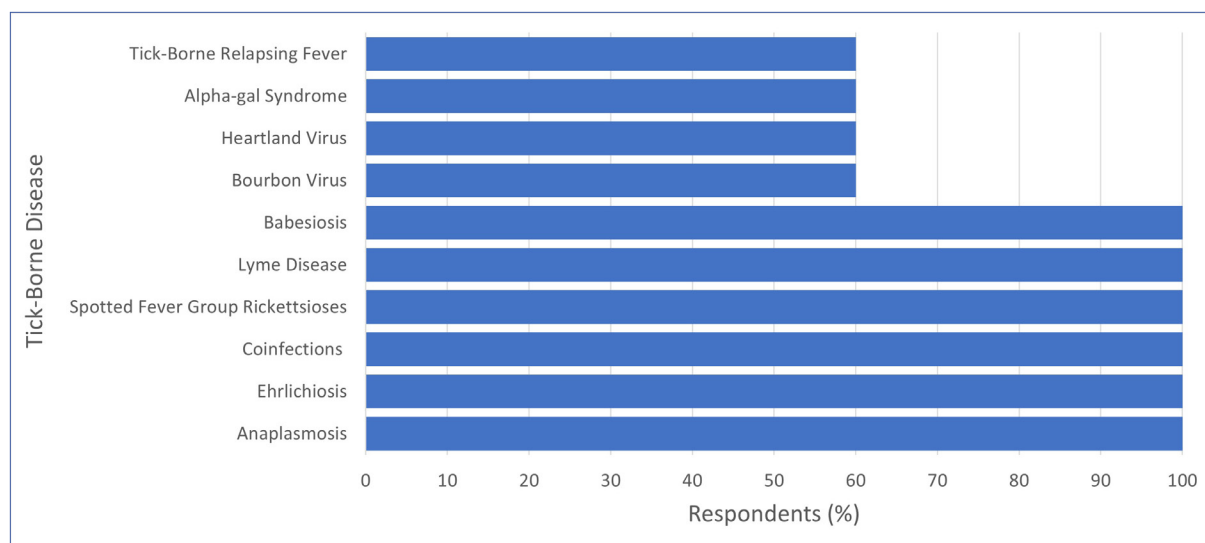


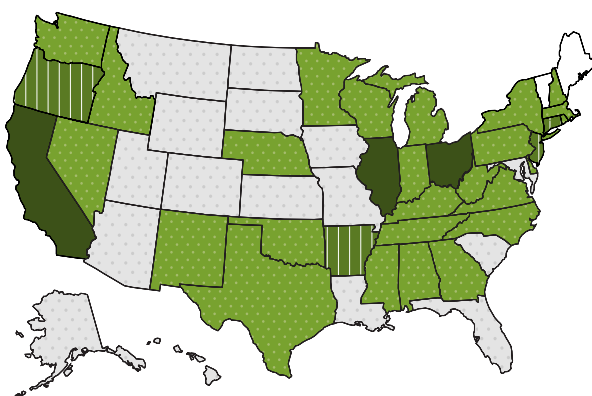
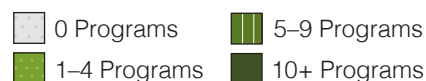
Figure 15. Tick-borne diseases of interest identified within state reports.

NACCHO Tick Surveillance and Control

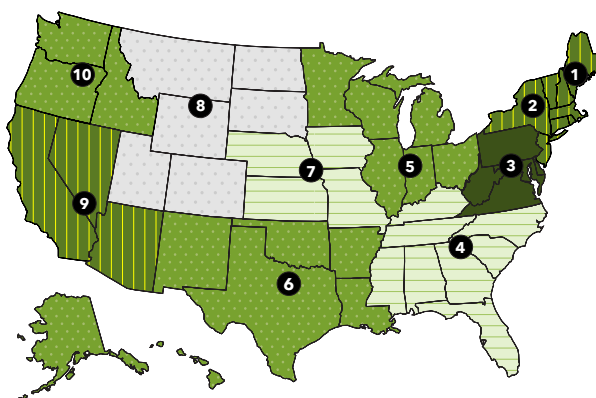
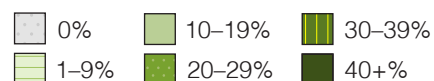
In its 2020 Vector Assessment Report, NACCHO included data on tick surveillance and control activity at the state, county, and local levels (NACCHO, 2020). This information on program capacity was collected through a survey of 483 respondents (103 of which completed the tick section of the assessment), including local health departments, mosquito control districts, and city and county departments, including state health departments, environmental health services, tribal programs, and public works. As with the state reports, relevant information is presented to supplement state response to tick-borne diseases and associated illnesses. Of note, several states responded to both the NACCHO survey and the National Inventory survey; therefore, data will overlap in some instances.

Figure 16 provides a breakdown of tick surveillance programs throughout the United States. Map A shows reported tick surveillance by state, and Map B shows the percentage of programs conducting tick surveillance by HHS region (1-10). (Tick surveillance data were not available from Maine or Vermont.) NACCHO also asked respondents about other types of tick-related activities they conduct. Of the 483 survey respondents, 35% reported engaging in public outreach and education campaigns related to tick-borne disease risk and prevention. In addition, 24% of respondents indicated that they offer in-house tick species identification services for the public, and 2% provide in-house tick pathogen testing, also for the public. However, only 21% of respondents reported conducting tick surveillance, and only 3% reported conducting tick control activities.



Map A: Tick Surveillance, by State

n=483

Map B: Percent of Programs Conducting Tick Surveillance, by HHS Regions 1 through 10

n=103

Figure 16. NACCHO tick surveillance maps by state (A) and HHS region (B)

[Source: NACCHO. (2020). *Vector Surveillance and Control at the Local Level: Findings from the 2020 Vector Control Assessment*. https://www.naccho.org/uploads/downloadable-resources/Vector-control_2020-assessment-report_Final.pdf]

Findings: Private Organizations Survey

Like the state survey, the survey of private organizations was new to the National Inventory. The survey was specifically tailored to collect data from U.S.-based private organizations that fund tick-borne disease research and activities related to the Working Group's priority issues. Broadly, the survey requested information related to the following categories:

- Annual funding and staffing
- Epidemiological activities
- Basic, clinical, and translational research within specified areas of interest
- Public-private sector collaboration
- Public engagement
- Future planning

Map A: Of the 103 programs that were engaged in tick surveillance activities, those located in California, Illinois, and Ohio were **most likely** to conduct tick surveillance—with 16, 14, and 12 programs in each state doing so, respectively.

Note: NACCHO does not have data for Maine and Vermont.

Map B: Of the 103 programs that were engaged in tick surveillance activities, those located in HHS Region 3 (Delaware, Maryland, Pennsylvania, Virginia, West Virginia) were **most likely** to conduct tick surveillance activities. Forty-seven percent of programs within this region reported tick surveillance activity.

Meanwhile, no programs located in HHS Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming) reported conducting tick surveillance activities.

The organizations were identified by soliciting names of the top funders from 2022 Working Group member, resulting in the following list of potential respondents:

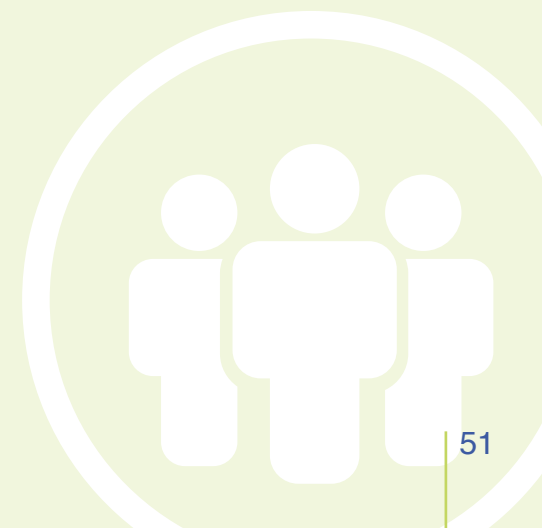
Bay Area Lyme Foundation	Lyme Disease Association
Cohen Foundation	Lymedisease.org
Global Lyme Alliance	LymeX Innovation Accelerator
LivLyme Foundation	Project Lyme

Methods

Points of contacts for each private organization were identified via the inventory advisory group. Those points of contact were invited to participate via an email that explained the objectives and timelines related to participation. Organizations received survey links on May 31 and given 3 weeks to complete the survey with the allowance for extensions on request. Reminder emails were sent 1 week prior to the deadline to ensure optimal participation rates. Seven organizations responded for an 86% participation rate.

Funding

Reported private tick-borne disease funding levels from 2018 to 2021 are reflected in Figure 17. Three private organizations did not disclose this information. Of those that responded, all reported a decrease in funding from 2020 to 2021. Two organizations explained that the reduction was due to the COVID-19 pandemic. One organization reported that a general decrease in donations necessitated a move to fundraising events online, hampering fundraising efforts. Another indicated that the pandemic caused many universities and grantees to delay or postpone their projects. Consequently, general funding was a fraction of their allowable budgets in 2020 and early 2021.



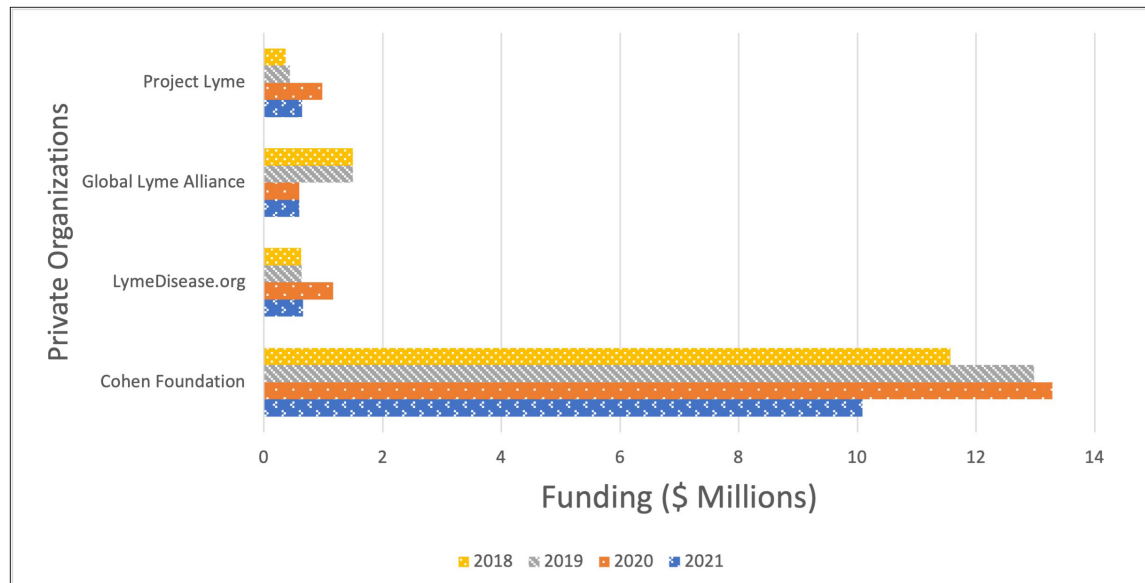


Figure 17. Reported funding for tick-borne disease research and related programs, FY2018–FY2021.

Staffing

Respondents were asked to report numbers of staff (0, 1–9, 10–19, 20–49, 50+). Results are reported in Table 6. One private organization reported having no full-time employees devoted to tick-borne diseases, relying instead on more than 50 support staff members, including contractors and fellows, to conduct the work. Four organizations reported having fewer than 10 staff supported with funds dedicated to tick-borne diseases.

Table 6. Private Organization Staffing Related to Tick-Borne Diseases and Associated Illnesses

	Full-Time Employees	Support Staff
Bay Area Lyme Foundation	<10	<10
Global Lyme Alliance	<10	0
LivLyme Foundation	0	<10
LymeDisease.org	<10	<10



	Full-Time Employees	Support Staff
LymeX	<10	0
Project Lyme	<10	<10
Steven & Alexandra Cohen Foundation	0	0

Programs and Activities

The first section of the survey was designed to collect data about each organization’s overall focus areas and to determine alignment of the programs and activities with the 2022 Working Group’s priority issues.

Figure 18 shows the percentage of organizations that fund research or conduct programs and activities in various categories related to tick-borne diseases and associated conditions.

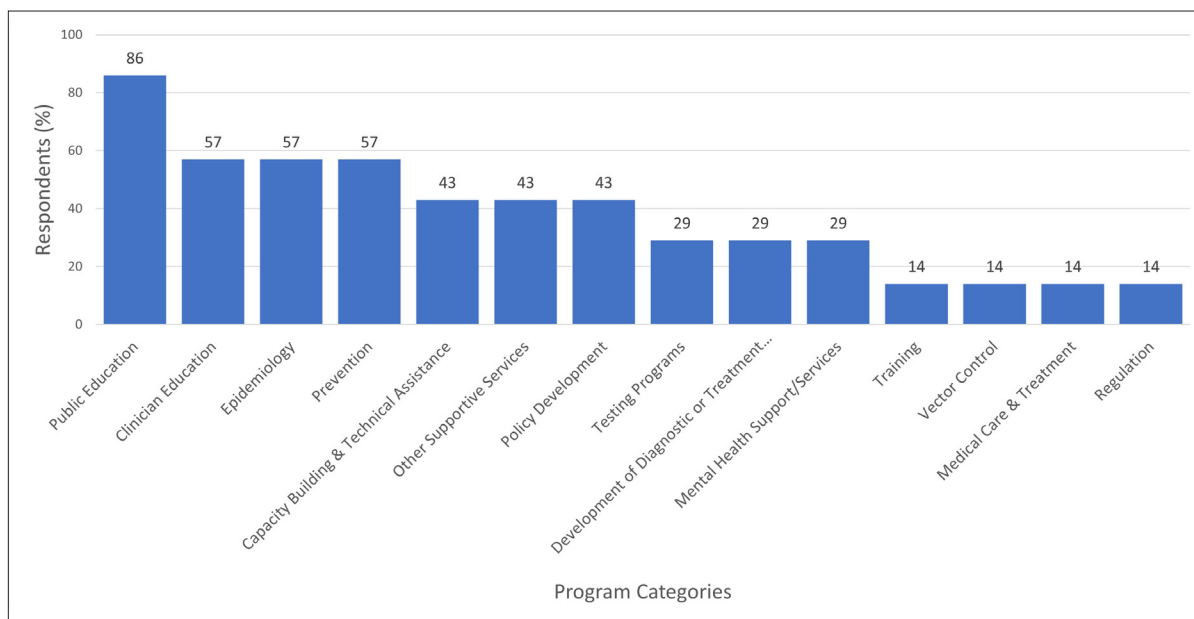


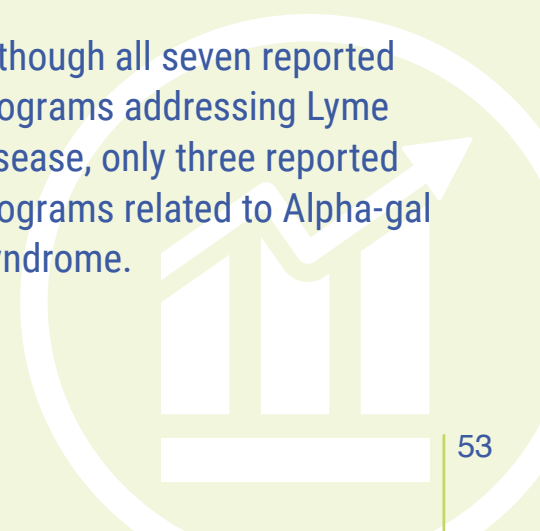
Figure 18. Programs related to tick exposure and tick-borne disease supported by private organizations.

Survey participants were asked to indicate which tick-borne diseases and associated illnesses were

No private organizations reported conducting or funding programs related to mental health services.

Six engaged in activities that expand knowledge and increase adoption of prevention activities through methods such as crowdsourcing, citizen science, public service announcements, tick distribution mapping, and app development.

Although all seven reported programs addressing Lyme disease, only three reported programs related to Alpha-gal Syndrome.



covered in their programs and activities. They were provided a comprehensive list of bacterial, parasitic, and viral infections, as well as other infections (i.e., STARI/Master's disease), coinfections and combinations of illnesses, and associated conditions, including AGS. Figure 19 captures the percentage of respondent activities devoted to specific illnesses.

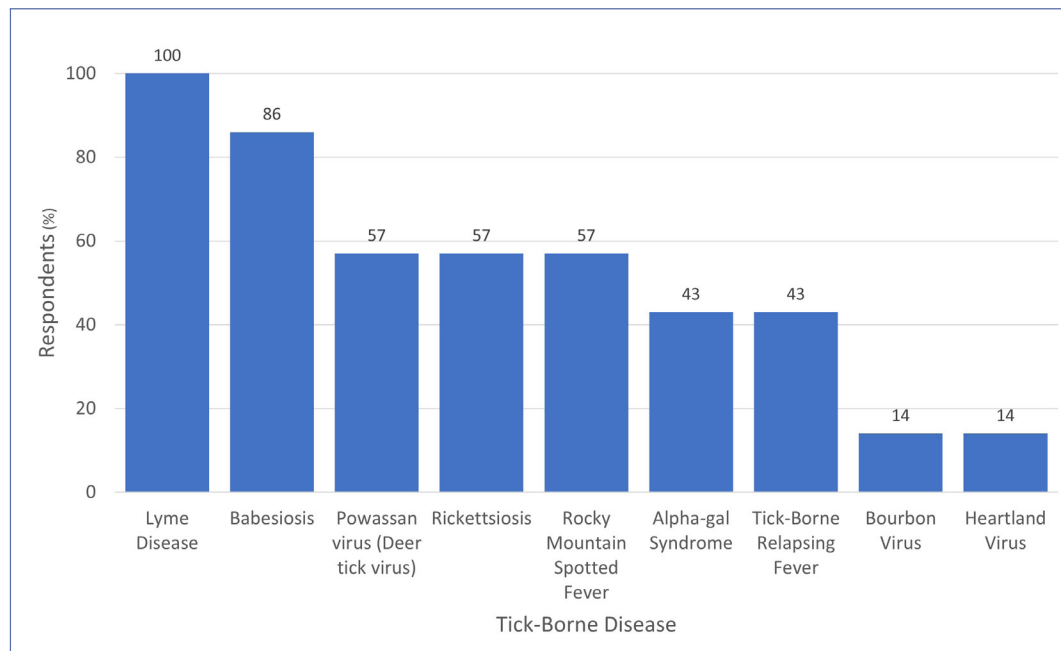


Figure 19. Tick-borne diseases and associated illnesses of interest to private organizations.

Like the federal and state surveys, respondents were asked to indicate how their programs and activities align with the themes of the Working Group's subcommittees and the issues they identified as most pressing. Their responses are reflected in Figure 20. Survey findings in each of these areas are described in the sections that follow.

Three private organizations reported AGS as a focus of projects or activities. No organizations reported work related to ehrlichiosis, anaplasmosis, bartonella, Bourbon virus, or Heartland viruses.



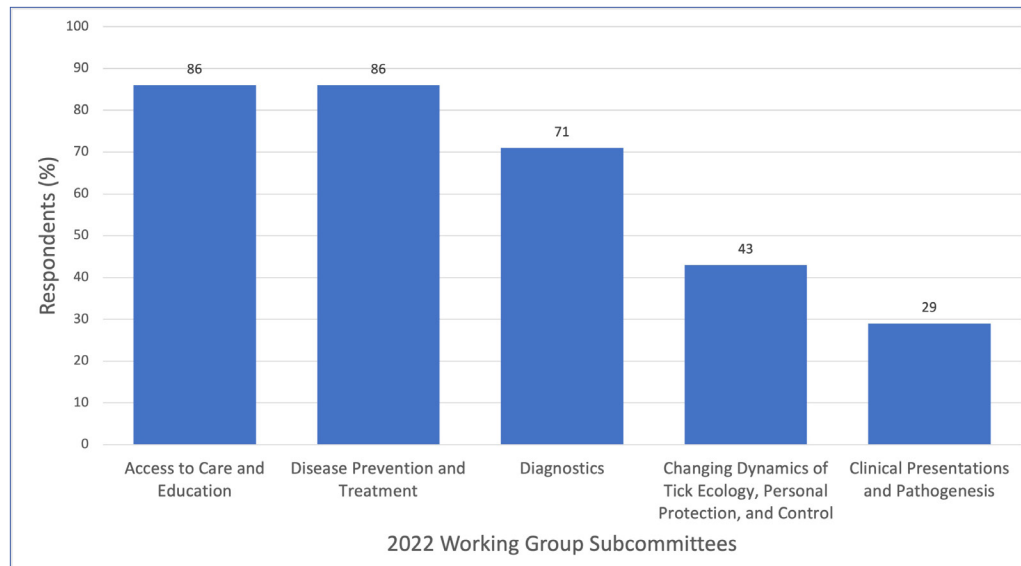


Figure 20. Private organization activities by 2022 Working Group subcommittee themes.

Health Equity

Health equity is a focus of private organizations as well as the Working Group (Figure 21). Private organizations were asked to indicate what groups received targeted funding. Most organizations indicated specific funding of programs and activities that focus on children. Half of the respondents reported targeted funding for high-risk workers (e.g., farmers, landscapers, and park employees). However, less funding was directed toward immigrant communities, pregnant people, Indigenous communities, communities of lower socioeconomic status, and people of color. No organizations fund or conduct programs targeting animal health professionals.



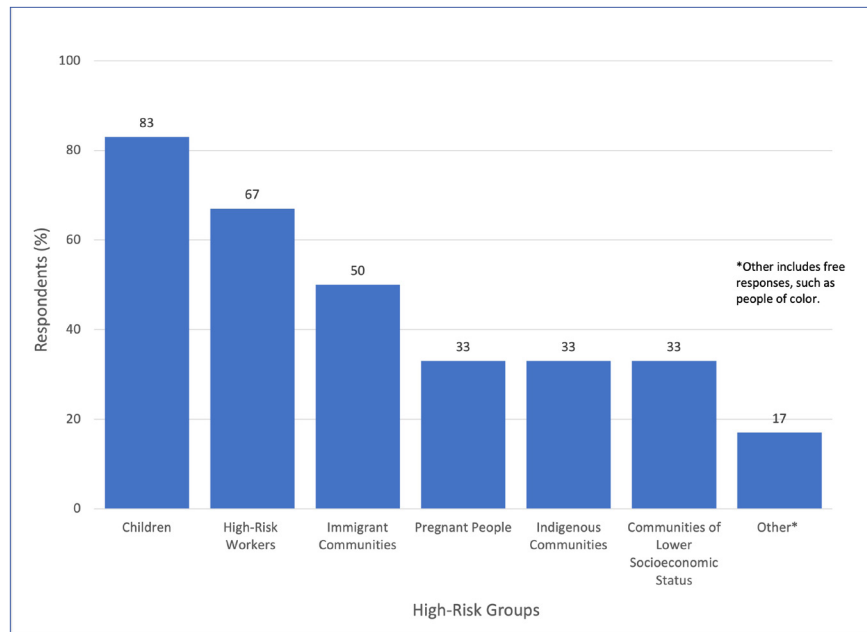


Figure 21. Private organization funding of high-risk groups, FY2018–FY2021.

Clinician and Public Education

Critical to successful patient outcomes is clinical education. Two organizations (29%) reported funding the development of training modules for health care providers about preventing, diagnosing, and treating LD. Another two reported developing similar content for other tick-borne diseases and associated conditions, including AGS and the impact of bartonellosis on high-risk patients, such as those experiencing homelessness and those who are immunosuppressed and/or immunocompromised.

Six organizations reported public education as a major focus area (86%). Two of them have developed modules or web content about AGS, with information about symptoms, avoidance measures, and an action plan for how to treat an allergic reaction (33%). One organization reported using crowdsourcing to create materials for tick bite prevention and general awareness (17%).

In addition, private organizations are actively involved in outreach and education to promote participation in scientific research. All seven respondents (100%) reported funding or conducting activities related to educating researchers, doctors, or disease advocates on the latest science, working hypotheses, or future research needs. Three organizations also engage the patient community about the benefits of participating in clinical studies (43%). Global Lyme Alliance created the TrialX Lyme Disease Symptom



Tracker, a phone application that enables individuals to search for clinical trials. Bay Area Lyme Foundation educates tick-borne disease patients about donating blood, urine, and tissue samples to the Lyme Disease Biobank. Finally, LymeDisease.org assists research and industry in patient recruitment and research enrollment.

Bringing Products to Market: Tick Bite Prevention, Tick Control, and Diagnostics

Private organizations are supporting the development and evaluation of tick control and tick bite prevention products through multiple means. Figure 22 shows how organizations fund or conduct activities in this area. Specifically, the Steven & Alexandra Cohen Foundation funds large-scale studies to assess two ecological interventions aimed at killing ticks that could lead to community-based health protection models. The LivLyme Foundation, through its TickTracker mobile phone application, is promoting the use of citizen science. LymeDisease.org is similarly using data from its application, MyLymeData, to conduct research, facilitate patient engagement, and assist researchers and industries recruit patients for studies.

Additionally, five private organizations reported funding programs to promote the evaluation and development of current and promising new diagnostic approaches. For example, LymeX Innovation Accelerator and the Steven & Alexandra Cohen Foundation fund the LymeX Diagnostics Prize Competition with a \$1 million prize pool, aiming to foster the development of diagnostics to detect active Lyme disease infections and enable premarket submission for FDA review. LymeDisease.org assists industries in patient recruitment for diagnostic studies in Lyme disease, while the Global Lyme Alliance has developed academic and business partnerships.

Two organizations fund programs that prioritize bringing new tick bite prevention or control products to market.

Three fund programs that facilitate commercialization of tick-borne disease intervention products.

Five fund the promotion, evaluation, and development of current and new diagnostic approaches through prize funds, cross-sector partnerships, and research grants.



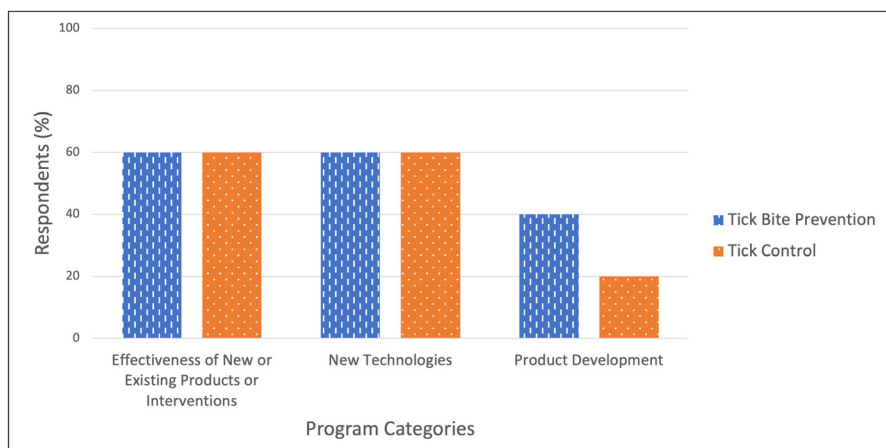


Figure 22. Technology development programs for tick bite prevention and tick control methods funded by private organizations.

Research

Research funding by private organizations covers a wide spectrum of areas related to tick-borne diseases and associated conditions. Figure 23 provides an overview of the research categories, and Table 7 outlines more specifically the types of research being conducted within those categories.

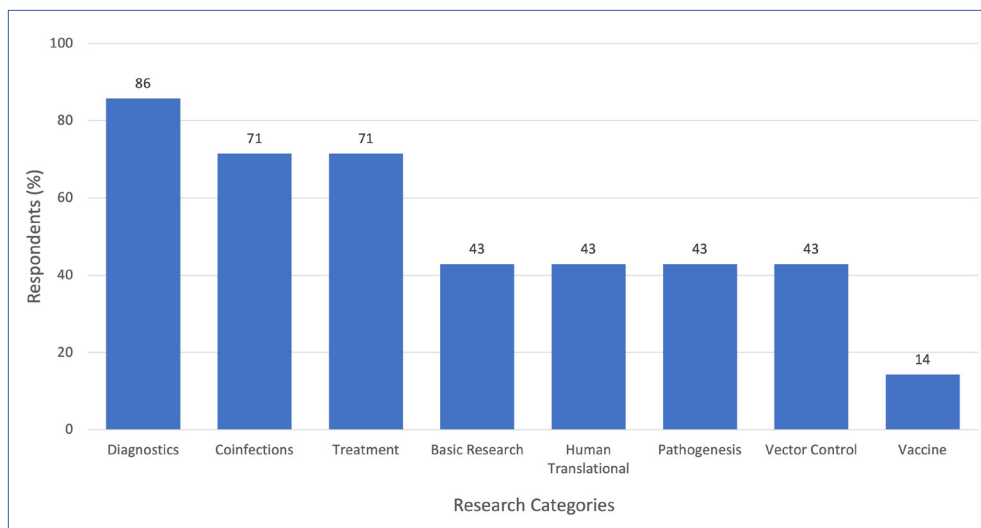


Figure 23. Categories of research funded by private organizations.



Table 7. Types of Research Funded or Conducted by Private Organizations

Categories and Subcategories	Number of Respondents
Tick and Pathogen Ecology	
Drivers of tick populations, tick pathogen prevalence, or geographic expansion of ticks and tick-associated diseases	3
Effectiveness of existing tick bite prevention strategies or products	1
Rapid identification of tick species and discovery of the pathogens they transmit	1
Collaborative Research	
Studies among investigators of different infection-related syndromes (e.g., shared mechanisms of disease between Lyme disease and other “long hauler” syndromes)	3
Health Equity	
Health equity in patients with tick-borne diseases and associated conditions	2
Prevalence of undetected tick-borne diseases among high burden of multi-systemic chronic conditions subgroups that may have been inadequately medically evaluated*	1
Longitudinal Studies	
Treatment efficacy or long-term effects of tick-borne diseases	2
Prevention	
“Anti-tick” human vaccines and novel tick-bite prevention methods	1
Effectiveness of existing tick bite prevention strategies or products	1
Treatment	
Antimicrobial compounds and antibody therapies for acute or persistent tick-borne disease infections, including Lyme disease	5
Therapeutic approaches for persistent post-treatment symptoms attributed to tick-borne diseases, including Lyme disease	5
Treatment and management of AGS	1
Treatment of neuropsychiatric disease related to Lyme disease or emerging vector-borne disease	1

Categories and Subcategories (continued)	Number of Respondents
Diagnostics	
Promising diagnostic technologies in tick-borne disease	6
Testing methodologies that detect different types and stages of Lyme disease (other than acute) or other elusive tick-borne infections	5
Identification of host immune markers to facilitate diagnosis	4
Clinical Presentation and Pathogenesis	
Causes of persistent symptoms attributed to tick-borne diseases, including Lyme disease	6
Full spectrum of clinical manifestations of tick-borne diseases and associated illnesses	5
Magnitude and outcomes of tick-borne disease coinfections	4
Clinical comparisons of long-hauler syndromes related to COVID-19 and Lyme disease	2
Magnitude and outcomes of vertical transmission of tick-borne diseases	2
Impact or mechanisms associated with tick-borne disease and pregnancy	2
Mechanisms leading to or perpetuating neuropsychiatric disease among individuals with Lyme disease or emerging vector-borne disease	2
Mechanisms of pathogenesis of tick-borne diseases, including longitudinal studies of post-treatment Lyme disease**	2
Women infected with Lyme disease during pregnancy and their offspring	2

*Multi-systemic chronic conditions include but are not limited to mental illness and musculoskeletal diseases; individuals who may be inadequately medically evaluated include individuals in psychiatric facilities, prisons, and homeless shelters, and other populations experiencing health disparities

**Central nervous system infection, including neuropsychiatric illness and neuropathic injury (2), persistent symptoms (1), and autoimmunity (1).

Although Table 4 provides a quick synopsis of research priorities and gaps, it is important to take an in-depth look at specific types of analysis initiated and supported in recent years. Private organizations, which have the capacity to be nimble and thus responsive to the needs of the tick-borne disease patient community, are often at the leading edge of research investment. This section features highlights of the valuable work conducted or funded in the private sector.

Health Equity

The majority of private funding organizations (57%) have been conducting research with health equity incorporated into research design, but more work is needed. Four organizations reported including a representative cross-section of patients from a variety of geographic, racial, ethnic, and socioeconomic backgrounds in their study design. Both the Steven & Alexandra Cohen Foundation and LymeDisease.org have studied the root causes of health disparities, and the latter has also analyzed intersectional issues. LymeDisease.org reported that access to care and structural barriers are a major organizational focus reflected in many of its publications.

Longitudinal Studies

By their very nature, longitudinal studies are difficult to achieve because they require considerable time, funding, and sustained participation. However, they are critical to understanding the long-term effects of tick-borne diseases and associated illnesses and to determining treatment efficacy, particularly in patients who are chronically ill. Two private organizations have succeeded in conducting or supporting longitudinal studies. Through its patient registry, LymeDisease.org has recruited more than 17,000 patients and published five peer-reviewed studies based on its data. In addition, the Cohen Foundation has invested in two epidemiology and risk factor studies on the effects of tick-borne diseases on individuals and vulnerable populations.

Biorepositories

Biorepositories are integral to tick-borne disease research. Collecting well-characterized human samples at different stages of disease is especially difficult without biomarkers and diagnostics for tick bite-associated chronic illness. Four private organizations fund the development of human biorepositories for human tick-borne disease samples.

Prevention

Several prevention activities funded or conducted by private organizations are outlined in the “Bringing Products to Market: Tick Bite Prevention, Tick Control, and Diagnostics” section of this report (p. 57). In terms of prevention-related research, the Steven & Alexandra Cohen Foundation has funded two types of prevention research: an anti-tick bite vaccine to help prevent transmission of multiple tick-borne diseases (Yale University) and a large-scale investigation of ecological interventions to kill ticks (Cary Institute).

Understanding the pathogenesis of Alpha-gal Syndrome has yet to receive private-sector investment.

Only one organization has funded activities related to the development of “anti-tick” human vaccines and novel tick-bite prevention methods to provide protection against multiple tick-borne diseases.

Pathogenesis

Private organizations have invested primarily in two focus areas related to pathogenesis: persistence and vertical transmission of tick-borne diseases, particularly Lyme disease. Four organizations reported funding research or conducting activities related to the mechanisms of persistence. Study topics included antibiotic tolerance, persistence of symptomology in Lyme disease patients and those with coinfections, central nervous system infection (including neuropsychiatric illness and neuropathic injury), biomarkers, and immunity. Collectively, these studies were funded by the Bay Area Lyme Foundation, Global Lyme Alliance, Project Lyme, and Steven & Alexandra Cohen Foundation. In addition, LymeDisease.org has assisted in enrollment efforts for two studies using novel approaches to identify biomarkers for Lyme disease.

Related to vertical transmission, the Steven & Alexandra Cohen Foundation reported funding a multi-disciplinary conference on congenital Lyme disease in June 2022. Further, LymeDisease.org conducts a survey addressing vertical transmission of tick-borne diseases through its MyLymeData platform.

Diagnostics

A major gap in diagnostics is the ability to detect various stages of Lyme disease. Four organizations reported funding or conducting research aimed at identifying host immune markers to facilitate diagnosis. For example, LymeDisease.org has assisted in enrollment efforts for two studies using novel approaches to identify biological markers for Lyme disease. In addition, the Steve & Alexandra Cohen Foundation has funded biomarker studies at the Institute for Systems Biology, Mt. Sinai, Johns Hopkins, and the University of California San Francisco. As described in the “Bringing Products to Market: Tick Bite Prevention, Tick Control, and Diagnostics” section of this report (p. 57), LymeX Innovation Accelerator has held competitions to foster the development of new diagnostics for Lyme disease.

The LivLyme Foundation has funded research at Stanford University to design a peptide microarray and aims to identify immunogenic sites that can detect different stages of Lyme disease.

Treatment

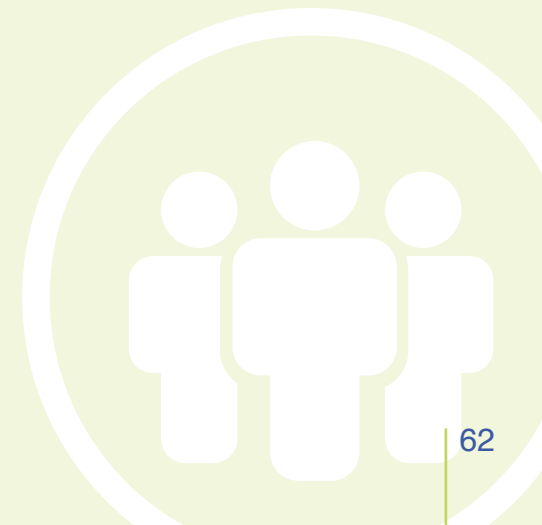
Individuals with tick-associated chronic illness are often without effective therapies, not only to treat infections, but also to alleviate their myriad and often debilitating symptoms. Therefore, treatment is an area that receives significant investment from private organizations. Four organizations provided the following details about their funding efforts in therapeutics. (Note: Bay Area Lyme Foundation indicated that its projects are subject to nondisclosure agreements.)

Biorepositories Funded by Survey Respondents

SLICE (Study of Lyme Disease Immunology and Clinical Events)—
Johns Hopkins University Lyme Disease Research Center Funder:
Steven & Alexandra Cohen Foundation

Lyme Disease Biobank Funder:
Bay Area Lyme Foundation and Project Lyme

Pedi Lyme Net—Boston Children’s Hospital Pediatric Lyme Network
Funder: **Global Lyme Alliance**



Global Lyme Alliance

Drug discovery research and R&D for Hygromycin A

LivLyme Foundation

- Identification of several antibiotics and their combinations to target *Borrelia* (University of New Haven)
 - Combining certain essential oils and antibiotics for more effective eradication of *Borrelia* persisters and biofilms (co-sponsored research)
-

LymeDisease.org

MyLymeData is a resource to help determine effective treatments

Steven & Alexandra Cohen Foundation

- Project to develop 16 therapeutics involving multiple universities: Duke University, Indiana University, Johns Hopkins University, Northeastern University, North Carolina State University, Tulane University, University of California San Diego, University of Maryland, and Yale University
 - Studies to test combinations of FDA-approved drugs targeting Lyme disease bacteria that may persist beyond the standard course of antibiotics
 - The Cohen Center for Health and Recovery from Tick-borne Diseases (CHAR) at Columbia University
 - Clinical Trials Network (Columbia University, Johns Hopkins University, Children's National Hospital)
-

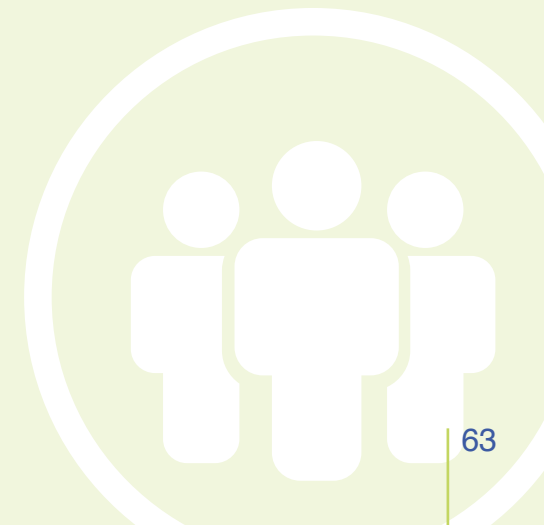
Other Tick-Borne Diseases and Lyme Disease Coinfections

The Steven & Alexandra Cohen Foundation was the only private organization to report funding for diagnostics and therapeutics research, specifically for bartonellosis, babesiosis, and other tick-borne diseases. In addition, the Cohen Center for Health and Recovery from Tick-borne Diseases at Columbia University treatment center provides treatment for coinfections.

Future Plans

The following list provides a broad overview of where private organizations intend to invest funds in the future.

- Education (Bay Area Lyme Foundation, LivLyme Foundation, LymeDisease.org, Project Lyme)
- Treatment (Bay Area Lyme Foundation, LivLyme Foundation, LymeDisease.org, Project Lyme)
- Diagnostics (Bay Area Lyme Foundation, LymeDisease.org, Project Lyme)



- Access to care (LivLyme Foundation, LymeDisease.org, Project Lyme)
- Disease prevention (LivLyme Foundation, LymeDisease.org, Project Lyme)
- Personal protection (LivLyme Foundation, LymeDisease.org)
- Public education (LivLyme Foundation, LymeDisease.org)
- Service members, veterans, and their families (LivLyme Foundation, LymeDisease.org)
- Changing dynamics of tick ecology (Project Lyme)
- Pathogenesis (LivLyme Foundation)

Four organizations also indicated that they plan to increase staffing to support tick-borne disease programming, activities, and research. Three organizations intend to expand relationships with industry partners and academic researchers. One organization plans to expand funding for clinical and employer education or research around clinical presentation.

Discussion: Survey Results and Limitations

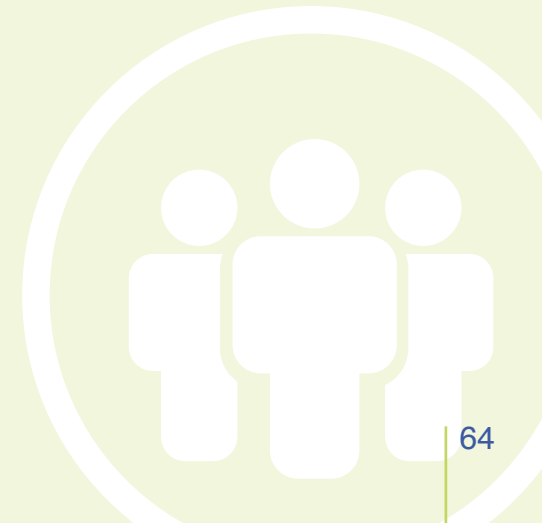
Considerable efforts are under way to address tick-borne diseases and associated illnesses across federal agencies and states and within private organizations. Several observed gaps and advances are described throughout the report. Federal agencies reported no funding and little research related to health equity specifically. CDC was the only agency to indicate any work on equity specific to tick-borne diseases. Although all agencies reported engaging in activities to increase adoption of tick-borne disease prevention or control methods, little work was reported concerning educating the public or health care providers. Furthermore, no agency reported identifying or implementing solutions that streamline the regulatory pathway for getting new tick-borne disease diagnostic offerings to market.

There appears to be considerable disparity regarding the programs and activities across states and regions. Nine states were invited to participate in the survey; however, only five responded. By using annual reports from an additional 10 states identified in the scoping, a clearer picture emerged. All responding states reported conducting human and vector surveillance as well as local and regional surveillance and reporting of tick-borne diseases. In addition, most states indicated some focus on both public and clinical education as well as education as prevention programs. All states reported funding or conducting programs and/or activities in public education, clinician education, epidemiology, and prevention.

Importantly, because of survey limitations, findings were skewed to states with the most funding and dedicated activities to tick-borne disease and associated illnesses. Furthermore, those states lacking infrastructure would not publish annual state reports. Indeed, NACCHO concluded from its Vector

“The Cohen Center for Health and Recovery from Tick-borne Diseases (CHAR) at Columbia University will provide innovative patient care to adults and children suffering from Lyme and tickborne disease. The Center is dedicated to treating acute and chronic forms of tickborne diseases with a combination of conventional and integrative approaches. To optimize patient care and enhance scientific learning, CHAR will also blend in clinical research studies to offer innovative diagnostic and treatment options to patients.”

—Steven & Alexandra Cohen Foundation



Control Assessment that most state programs surveyed were not engaged in any tick control or surveillance activities or any education or outreach related to education. Furthermore, regions appear starkly disparate, with some regions conducting no or very little surveillance related to tick-borne diseases. As a national survey, NACCHO's assessment provides beneficial insight into those states not included in this report. Taken together, significant gaps in state activities relating to tick-borne diseases are apparent. Further investigation to quantify and characterize these gaps is warranted.

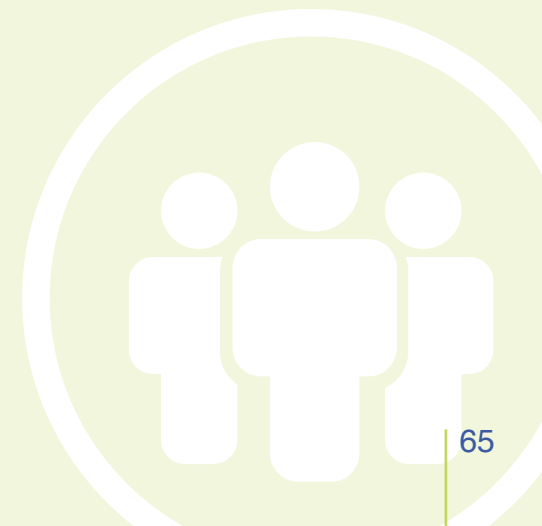
Private organizations are investing significantly in multiple areas in tick-borne disease and associated illnesses. Private organizations are overwhelmingly funding activities related to Lyme disease and babesiosis, with more than half also contributing to RMSF, Rickettsioses, and Powassan virus. No private organization reported providing support for tick-borne related illnesses such as Q fever, tick-borne relapsing fever, or Heartland virus, among others. Furthermore, more than half of the private organizations reported providing support for health equity with a focus on children and at-risk workers. Five organizations reported supporting programs relating to tick ecology, control, and personal protection, with the majority funding programs focused on children and high-risk workers, and few supporting communities with lower socioeconomic statuses, Indigenous populations, or pregnant peoples.

"With future federal funding, we hope to expand our diagnostics prize competition purse and increase our spending on education and awareness innovation."

—LymeX Innovation Accelerator

"We believe that there is a strong need to develop research capacity within the community and to develop community-based participatory research models."

—LymeDisease.org



Chapter 5: Discussion

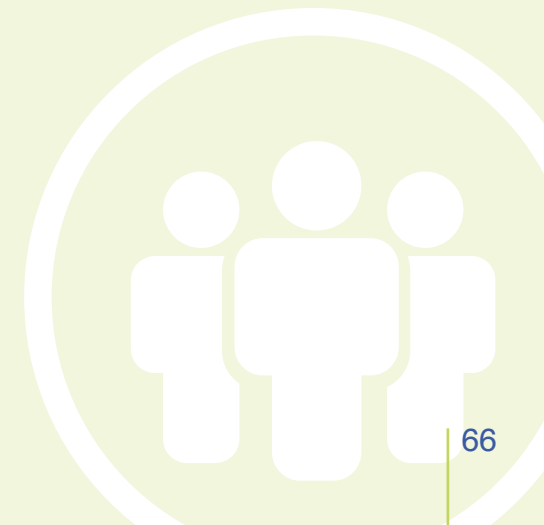
The tick-borne disease field is exceptionally complex and highly nuanced. Each individual tick, pathogen, and disease represents a standalone field of study. Moreover, every state faces its own unique challenges because pathogen prevalence and disease incidence vary greatly, even at the county level. Consequently, an appropriate collective response to tick-borne diseases and associated illnesses as a significant health issue requires an interdisciplinary approach to designing and applying research and preventing, treating, and caring for the American public. Greater participation and information sharing by federal agencies, states and local entities, and private funding organizations, is needed to address this immense challenge.

The scoping review revealed the extent, range, and nature of research activities of tick-borne diseases and associated illnesses in the United States. The literature review highlighted areas of emerging investigation to provide an annotated description of the trajectory of tick-borne disease research. One limitation of the review was the omission of international literature. Given the impact of tick-borne diseases in countries outside of the United States, further insight could be gained from an international perspective; a future inventory could be broadened to include international programs, activities, and research.

Attempting to analyze the research categorically proved challenging because of the large amount of topic areas and issues that overlap or apply to multiple categories of tick-borne diseases. However, themes did emerge from the scoping review. In general, tick-borne disease research is steadily increasing each year. Most of the published and ongoing research is focused on surveillance of ticks and tick-borne disease, diagnosis and diagnostics, and prevention, particularly as they relate to Lyme disease. The published literature demonstrates some advancing research in the treatment of Lyme disease and Lyme disease–associated chronic illness, as well as in the knowledge of the pathogenesis of this illness. Noteworthy studies include the investigation of *B. burgdorferi* persistence and immune function related to *B. burgdorferi* infection. However, there is a lack of ongoing treatment and diagnostic research focused on tick-associated illnesses other than Lyme disease.

Equity and Access to Care

More work is needed to improve understanding of the contributing factors of tick-borne disease burden. Research related to access to care and disease burden, particularly among underserved communities and at-risk populations, is inadequate. For example, Hispanic individuals are underrepresented in both published and unpublished tick-borne disease research, and few studies examine race and ethnicity. Current studies have identified that children, pregnant people, older adults, those with limited health care, outdoor workers, people with financial strain, Indigenous communities, and people of color, including



people of Hispanic origin, are more vulnerable to tick exposure and tick-borne diseases. However, limited studies explore health outcomes in these populations and are prone to sample bias.

Importantly, the literature suggests that increased access to education for both individuals and health care providers regarding the risks of tick exposure, as well as the signs and symptoms of tick-borne diseases, may increase diagnostic accuracy and reduce time to access health care. In turn, hospitalization rates and costs associated with tick-borne diseases could be reduced. State surveys identified that children are the primary focus of programs aimed to prevent tick bites or mitigate disease, or are otherwise equity oriented; however, other vulnerable populations are underrepresented within these programs. For example, few states support programs aimed at preventing tick bites in high-risk workers and immigrant populations. Enhanced education and prevention programming for vulnerable populations could significantly reduce the overall burden of tick-borne diseases and associated illnesses.

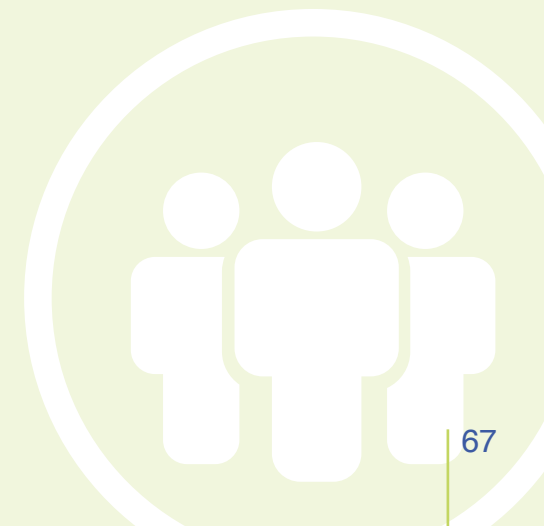
Although most private funding organizations are conducting research with health equity incorporated into research design, 43% are not. Federal and state surveys identified similar trends. Few agencies reported activities related to populations typically affected by health equity issues. New York, Pennsylvania, CDC, and NIH support research involving people of lower socioeconomic status and from a variety of ethnic backgrounds. Pennsylvania also provides training modules for tick-borne diseases including materials on different racial groups. New Jersey and CDC support programs focused on immigrant populations, while USDA supports programs focused on Indigenous populations. Furthermore, DoD and NIH support tick-borne disease research involving pregnant people. Maine, West Virginia, and FDA did not report supporting programs focused on health equity or vulnerable populations.

A growing focus surrounding health equity is expected in the coming years. Health equity has become a major focus of the federal government, as underscored in the 2021 [Executive Order on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government](#).

All tick-borne disease research should be designed within an equity lens, so that appropriate evaluation can occur. To ensure it exists for all, health equity must be woven into the planning and execution stages of all tick-borne disease activities, including research, surveillance, prevention, diagnosis, and treatment. These gaps are not restricted to tick-borne-disease research; rather, they reflect the issues surrounding inequities in the health arena and broader society.

State Data

Because of survey restrictions and time constraints, a full national survey of states was not possible. Consequently, the state survey results present information provided by five states. Given that the sample size was small and that states were chosen based on the incidence of tick-borne diseases, infrastructure,

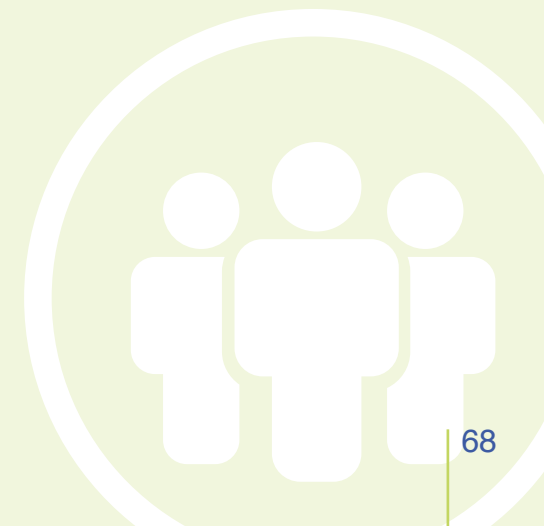


programs, and funding, findings cannot be extrapolated to the country and are generally skewed toward states with the most funding and dedicated activities to tick-borne disease and associated illnesses. By using annual reports from an additional 10 states identified in the scoping review, a clearer picture emerged. All responding states report conducting human and vector surveillance at the state, regional, and local levels. In addition, most states indicated some focus on both public and clinical education as well as education as prevention programs.

However, based on all data sources, considerable disparity exists in the types of programs and activities conducted across states and regions. Those states with the least infrastructure did not publish annual state reports and consequently are not included in this report. NACCHO concluded from its 2020 Vector Control Assessment that most programs surveyed were not engaged in any tick control or surveillance activities or any education or outreach related to education. Furthermore, regions appear starkly disparate, with some regions conducting no or very little surveillance related to tick-borne diseases (NACCHO, 2020). As a national survey, the NACCHO assessment provides beneficial insight into those states not included in this report.

Taken together, significant gaps in state activities relating to tick-borne diseases are apparent. Further investigation to quantify and characterize these gaps is warranted. This information gap leaves clinicians and the public undereducated about the true risk of tick-borne diseases and associated illnesses in these areas. Through the Tick-Borne Disease Working Group's public comments process (2018–2022), individuals from southern states have repeatedly written letters and provided verbal comments about their inability to access care in their states because of a general lack of awareness that tick-borne diseases occur there (Tick-Borne Disease Working Group, 2022). Furthermore, Arizona has seen an increase in RMSF cases in recent years. Between 2002 and 2021, more than 500 cases and 28 fatalities were reported (CDC, 2022). These cases have occurred primarily in Tribal communities, and approximately half of the deaths occurred among children (CDC, 2017). The high disease burden in Arizona underscores the need for states to actively track, report, and share surveillance data and best practices, so that other states and the federal government can better understand the risks and take appropriate action.

Currently, no standardized approach exists to measure state or agency performance regarding tick-borne disease. Consequently, it is difficult to distinguish areas of appropriate performance and areas requiring improvement within state and federal tick-borne disease programs. One suggestion is to develop a roadmap for states that provides guidance and measurable performance indicators to track success in the progress against tick-borne disease. This framework could include assessment in domains such as surveillance, education, and prevention measures, which states may use to compare their performance against other states and across time within their state, and to provide readily available information to the public for a clear depiction of longer-term progress against tick-borne disease. This roadmap could also be used to identify gaps where funding allocation is necessary. For example, if a state scores poorly in



an area such as surveillance, funding could be allocated toward this domain. This framework may be developed by modifying existing tools such as The Commonwealth Fund's *2022 Scorecard on State Health System Performance*, which assesses five dimensions on state performance based on 56 performance indicators (The Commonwealth Fund, 2022). This model could be adapted to evaluate performance in the domain of tick-borne disease based on determined dimensions and performance indicators. Another example is the National Public Health Performance Standards, which assesses Public Health Systems at the state and local levels. Here, performance measures are evaluated with a series of questions relevant to each measure (National Association of County and City Health Officials, 2013). These examples demonstrate ways in which assessments can effectively inform progress in health systems.

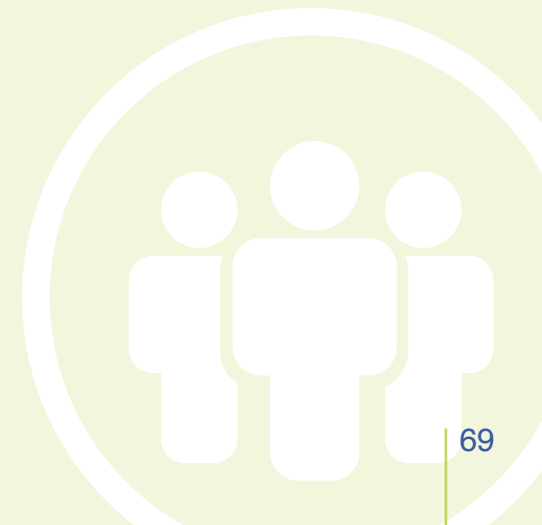
Suggestions for Future Research

The report generated additional suggestions that could improve the inventory process in the future. By responding to the limitations of this National Inventory, such as the development of a roadmap for states discussed above, a clearer understanding of progress within the tick-borne disease landscape in the United State would occur.

Wide disparities in infrastructure, programming, and funding exists across states and regions; a truly national survey of states could generate a better understanding of interstate differences. In future cycles, collection of comparable data from all states and territories would enable the establishment of a national baseline from which to measure progress, draw informed conclusions, and target initiatives for underserved states and regions.

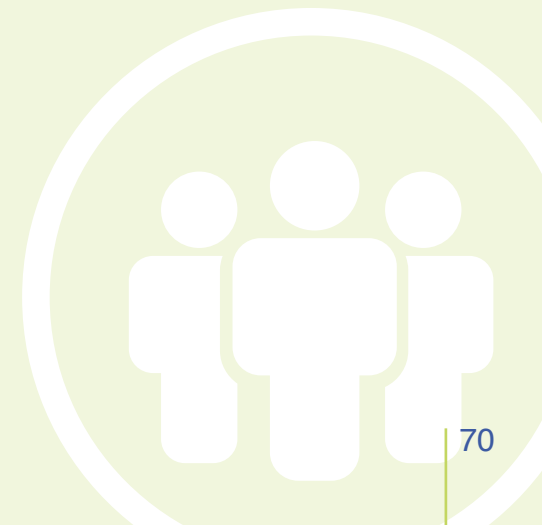
Surveys were developed for each category of respondents; however, some participants noted that surveys were not optimal in the current form. The private organization survey was well received and effectively provided an overview of activities, research, and funding. However, with the cross-division information reporting required of some states and agencies, a streamlined online survey was found to be onerous for some. Future surveys should be refined to reflect the feedback received and implement a further tailored survey for those organizations that require transmission of larger amounts of data. Once revised, pre-testing of survey instruments should occur to minimize the workload for participation while maintaining an optimal level of data collection.

Lengthening the time for data collection would also encourage increased agency and state participation. Requesting data at certain times of the year with a small response time is an onerous task for state health departments and laboratories particularly when staff must prioritize outbreaks and pressing health issues. For example, states were asked to complete the survey during the summer months and during a monkey pox outbreak, which undoubtedly reduced the state participation rate.



Future collection of the CMS data would further inform the tick-borne disease knowledge base. Although not a realized goal of this report, a pilot feasibility study was developed and serves as a strategy to analyze reimbursement costs from CMS Medicare data to broaden the acumen of this objective.

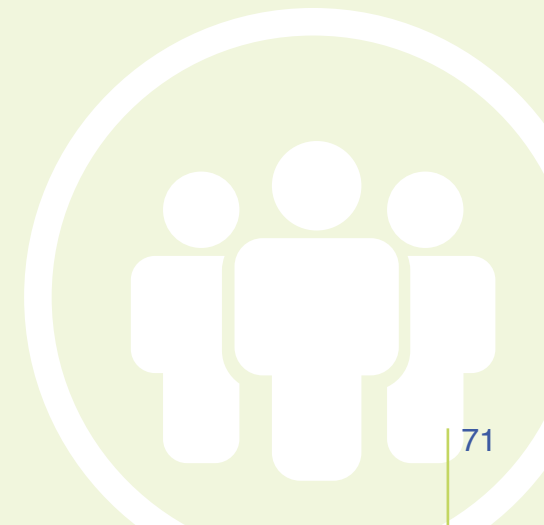
Although difficult to quantify, the impact of the pandemic on the results is evident in some instances. For example, all private organizations that provided funding levels reported significant drops in funding caused by the pandemic. In addition, closures of laboratories and universities and halting of conferences and clinical trials undoubtedly had an impact on research and resultant publications. The volume of literature would have likely been higher absent the pandemic. Future inventories would aid in reducing the “data noise” caused by the pandemic by providing a longitudinal view of progress.



Chapter 6: Conclusion

This was the first year the Working Group's federal inventory was national in scale. The state and private organization surveys, the scoping literature review, and the development of CMS data collection framework were novel. This cycle also built on the significant work of previous and current Working Groups by developing a schema derived from Working Group subcommittee report topics. This process provided an informed methodology to examine advances, overlaps, and gaps in the response to tick-borne diseases and associated illnesses across the nation. What emerged was a reliable framework for this cycle and future inventories.

Immense challenges remain to mitigate the increasing risk of tick-borne diseases in the United States. Findings suggest that considerable work is occurring across federal agencies and states, through private organization efforts, and in various research fields. However, considerable gaps in certain areas of research and inconsistent funding are evident, and more work is needed to ensure equitable access to the knowledge base and to tools for tick-borne disease prevention, diagnosis, and treatment. It is hoped that this report meets its objective as an inventory to inform the Working Group and the wider audience and serves as a framework for future initiatives to track progress against tick-borne diseases nationally. With increasing awareness and directed efforts, the nation can reduce existing gaps and advance our common goal to have a nation free from tick-borne diseases and associated illnesses.



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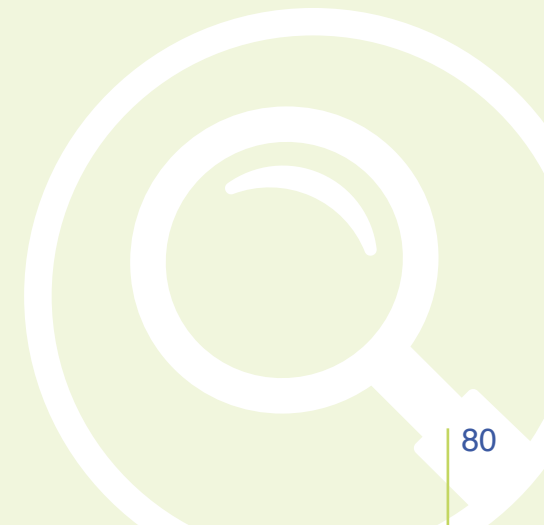
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APPENDIX B: Abbreviations and Acronyms

Acronym/ Abbreviation	Definition
AGS	Alpha-gal Syndrome
CDC	Centers for Disease Control and Prevention
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMS	Centers for Medicare & Medicaid
DoD	U.S. Department of Defense
ELISA	enzyme-linked immunoassay
FDA	U.S. Food and Drug Administration
FY	fiscal year
GC-FP	Grating Coupled-Fluorescent Plasmonic
IgG	Immunoglobulin G
NACCHO	National Association of County and City Health Officials
NIH	National Institutes of Health
NSAIDS	non-steroidal anti-inflammatory drugs
OASH	Office of the Assistant Secretary for Health

Acronym/ Abbreviation	Definition
OIDP	Office of Infectious Disease and HIV/AIDS Policy
PCR	polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTLD	Post treatment Lyme Disease
QoL	quality of life
RMSF	Rocky Mountain spotted fever
SERDP	Strategic Environmental Research and Development Program
STARI	Southern Tick-Associated Rash Illness
TBE	tick-borne encephalitis
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
VTA-ESR	Vertical Tick Assay for Evaluation of Spatial Repellents
Working Group	Tick-Borne Disease Working Group

APPENDIX C

Private Organizations Survey

Hyperlink to URL (to come)

State Survey

Hyperlink to URL (to come)

Federal Agency Survey

Hyperlink to URL (to come)

Catalog of Published Literature

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