Tick-Borne Diseases and Associated Illnesses:
Updated Scoping Review

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Introduction

In 2022, a scoping review was conducted to gain a comprehensive perspective of research on tick-borne diseases and associated illnesses. The review, encompassing both published and unpublished literature, was designed to provide an independent assessment of the research environment in the United States and to identify gaps, advances, and overlaps, particularly in priority areas identified by the 2022 Tick-Borne Disease Working Group and its subcommittees.

Building on this foundation, the current updated review extends from July 1, 2022, to December 31, 2023. This updated analysis delves into the developments, emerging trends, and crucial insights within tick-borne diseases and associated illnesses research during this period, focusing exclusively on published literature. This updated review complements the previous analysis, which covered the period from January 1, 2018, to June 30, 2022.

The review is conducted as part of the Tick-Borne Diseases and Associated Illnesses: National Community Engagement Initiative, administered by the U.S. Department of Health and Human Services Office of Infectious Disease and HIV/AIDS Policy in partnership with the Office of the Assistant Secretary for Health, the Centers for Disease Control and Prevention (CDC), the Centers for Medicare & Medicaid Services, the U.S. Department of Defense, the U.S. Food & Drug Administration (FDA), the National Institutes of Health, and the U.S. Department of Agriculture. In addition to this updated scoping review and an international literature review, the initiative includes a series of community engagement sessions and public meetings, as well as a 2025 national inventory involving surveys of federal agencies, all 50 states and territories, and nonprofit organizations.

Methods

The scoping review is an overview of the landscape of literature concerning human tick-borne diseases and associated illnesses (e.g., Alpha-gal Syndrome [AGS]) in the United States from July 1, 2022, through December 31, 2023. The review 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 (Page et al., 2021). The review included a search for national research related to specific themes, with the goal of scoping existing published 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 1, the inclusion and exclusion criteria were developed to set the parameters for the scoping review. The list of tick-borne diseases and associated illnesses included AGS, anaplasmosis, babesiosis, Bourbon virus disease, Colorado tick fever, ehrlichiosis, Heartland virus disease, Lyme disease, Powassan virus, southern tick-associated rash illness (STARI), spotted fever group rickettsioses (including Rocky Mountain spotted fever [RMSF]), tick-borne relapsing fevers, tularemia, and tick-borne disease coinfections (including bartonellosis and mycoplasmosis).

Similar to the previous scoping review, studies had to report on specific themes to meet the inclusion criteria. The themes were clinical presentation and pathogenesis, prevention, treatment, surveillance (tick, pathogen, and human disease), diagnosis and diagnostics, and duration of illness of tick-borne diseases and associated illnesses in humans in the United States. Also included for this updated scoping review were studies on climate change, integrated tick management, clinician education and awareness, and public education and awareness. These topics were frequently identified by experts who participated in the Tick-Borne Disease Working Group and their subcommittees as important factors and approaches to consider when developing strategies to tackle tick-borne diseases and associated illnesses.

Like the previous scoping review, 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.

Table 1. Scoping Review of Literature: Inclusion and Exclusion Criteria

Inclusion Criteria
Any research article published in the United States that discusses the following tick-borne diseases and associated illnesses: Alpha-gal Syndrome (also known as alpha-gal allergy or red meat allergy), anaplasmosis (*Anaplasma phagocytophilum),* babesiosis (*Babesia divergens, Babesia duncani, Babesia microti,* MO-1 [currently unnamed strain]), Bourbon virus disease (Bourbon virus, genus *Thogotovirus*), Colorado tick fever virus (genus *Coltivirus),* ehrlichiosis (*Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis),* Heartland virus disease (Heartland virus, genus *Bandavirus*), Lyme disease (also known as Lyme borreliosis; *Borrelia burgdorferi),* Powassan virus (also known as deer tick virus, genus *Flavivirus*), southern tick-associated rash illness (also known as STARI or Master's disease, causative agent unknown), spotted fever group rickettsioses including Pacific Coast tick fever (*Rickettsia philipii*), Rocky Mountain spotted fever (*Rickettsia rickettsii*), *Rickettsia parkeri* rickettsiosis (*Rickettsia parkeri*), tick-borne relapsing fevers including soft tick relapsing fever (*Borrelia hermsii*), hard tick relapsing fever (also known as *Borrelia miyamotoi* disease, *Borrelia miyamotoi),* tularemia (*Francisella tularensis*), tick-borne disease coinfections (two or more tick-borne diseases and associated illnesses, including bartonellosis [*Bartonella henselae*] and mycoplasmosis [genus *Mycoplasma*]—the two of which should only be included if they occur as a coinfection with a disease or illness caused by a tick bite)
Any article published in the United States that describes information related to tick-borne disease and associated illness: climate change, clinician education, diagnosis, diagnostics, duration of illness, etiology, health equity, integrated tick management, One Health approach, prevention, public education and awareness, surveillance (tick, pathogen, and human disease/illness, including community and/or citizen science approaches to tick surveillance), treatment
Any research article published in the United States that describes information related to tick-borne diseases and associated illnesses during blood transfusions, blood donations, and organ transplants
Published in the United States: Case studies, case reports, guidelines, and systematic reviews about tick-borne diseases and associated illnesses
Published U.S. state reports (to supplement state surveys)
Available in the English language
Publications dating from July 1, 2022, through December 31, 2023
Exclusion Criteria
Unpublished literature
Editorials, reviews, comments, replies, correspondences, viewpoints, and protocols
Research articles related to flea-borne diseases only
Research articles related to tick-borne diseases or associated illnesses published outside the United States
Research articles related to tick-borne diseases and associated illnesses in animals
Research articles related to zoonotic transmission of tick-borne diseases and associated illnesses

Search Strategy

A literature search was conducted using the PubMed database for studies published between July 1, 2022, and December 31, 2023. This approach differs from the previous review, where multiple databases, including CINAHL and Embase, were searched. The decision to focus solely on PubMed was made to streamline the process and reduce the number of duplicative results observed in the last review. While this approach may limit the inclusion of studies indexed in other databases, it enables a more focused analysis of the most relevant literature. A PRISMA flowchart of the study selection process is presented in Figure 1. Using the search strategy identified, 786 articles were generated and screened for eligibility. Title, abstract, and full-text review reduced the total to 173 published articles.
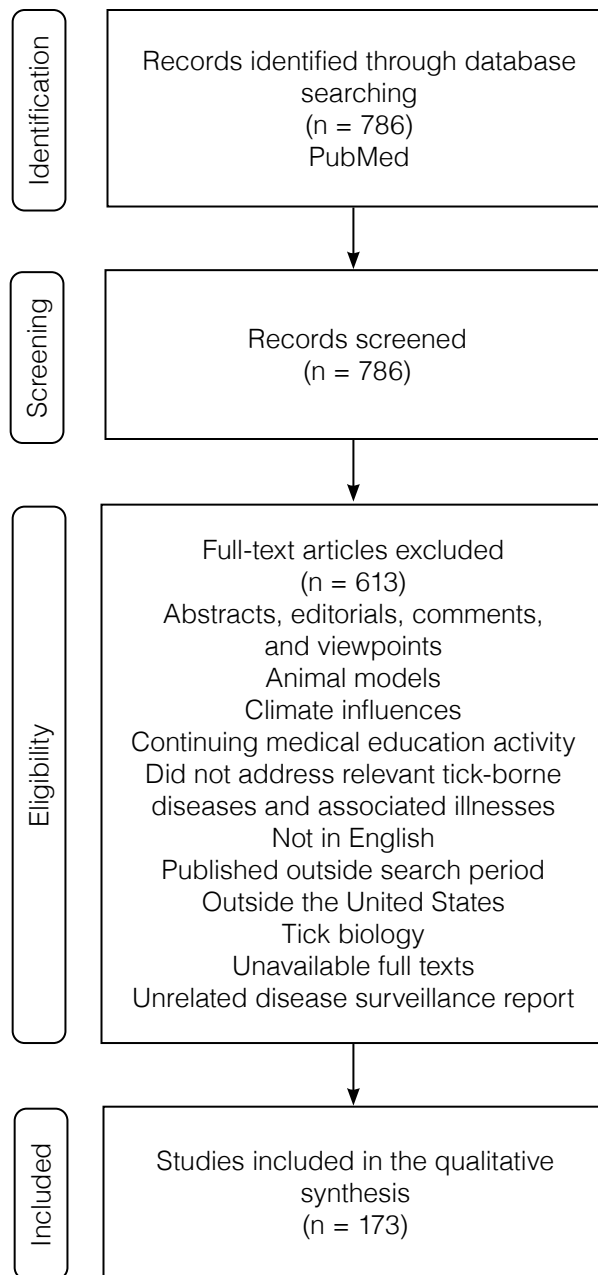
Records identified through database searching
(n = 786)
PubMed

Records screened
(n = 786)

Full-text articles excluded
(n = 613)
Abstracts, editorials, comments, and viewpoints
Animal models
Climate influences
Continuing medical education activity
Did not address relevant tick-borne diseases and associated illnesses
Not in English
Published outside search period
Outside the United States
Tick biology
Unavailable full texts
Unrelated disease surveillance report

Studies included in the qualitative synthesis
(n = 173)

Identification · Screening · Eligibility · Included

Figure 1. PRISMA flowchart of the study selection process.

Findings: A Snapshot of Published Literature

The primary objective of the scoping review was to provide a "bird's eye view" of published literature on tick-borne diseases and associated illnesses in the United States. The review focused on identifying gaps, advances, and overlaps occurring in domestic tick-borne disease research, to determine whether there have been changes in the emphasis in research areas over the 6-year period and whether publications have continued to increase, decrease, or remain unchanged. 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 July 1, 2022, through December 31, 2023, were cataloged. As an update of the initial review conducted in 2022, this review enables a characterization of literature over 6 years (January 1, 2018–December 31, 2023). Consequently, where appropriate, data are combined with the prior

scoping review to provide information on trends in specific areas of research and tick-borne disease research more broadly. Of note, the updated review spans a shorter timeframe than the previous review (18 months versus 4.5 years); this difference is accounted for in the analysis and discussion of the scoped literature.

Combined analysis by theme in the published literature over the 6-year period showed that apart from 2019, publications meeting the inclusion criteria have increased each year (Figure 2). Over the 6 years, 2019 had the fewest publications (58), and 2023 had the most (110). The prior review projected 82 publications for 2022. However, the actual number of publications exceeded this estimate, reaching a total of 99 for the year based on the same criteria (OASH, 2022). This positive trend of steadily increasing research across all categories illustrates expanding interest in the area of tick-borne diseases and associated illnesses.
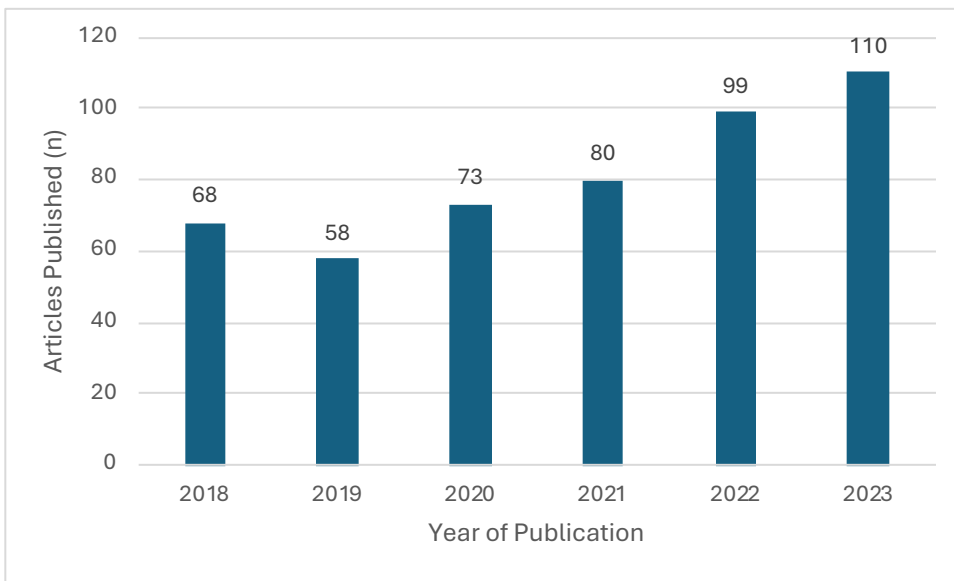

Figure 2. Total tick-borne disease articles published from January 1, 2018, to December 31, 2023.

Figure 3 details the distribution of themes in the updated review, showcasing significant shifts compared to the previous scoping review. In this latest review, 46% (79/173) of the articles address the clinical presentation and pathogenesis of tick-borne diseases and related illnesses, marking a notable increase from the previous focus on diagnostics. Studies on diagnosis and diagnostics constitute 17% (29/173). Surveillance-related articles account for a total of 24% (42/173), with pathogen surveillance at 11% (19/173), tick surveillance at 7% (12/173), and human disease surveillance at 6% (11/173). This shift indicates a growing emphasis on pathogen and tick surveillance relative to the earlier review. Treatment of tick-borne diseases and associated illnesses, previously identified as a major gap, remains covered in only 4% (7/173) of the articles. The updated review also introduces new themes, such as climate change, which were not prominently addressed in the earlier review. Prevention, clinician education and awareness, public education and awareness, integrated tick management, and climate change each appear in less than 5% of the articles, suggesting these areas are emerging but still underrepresented compared to previous topics.
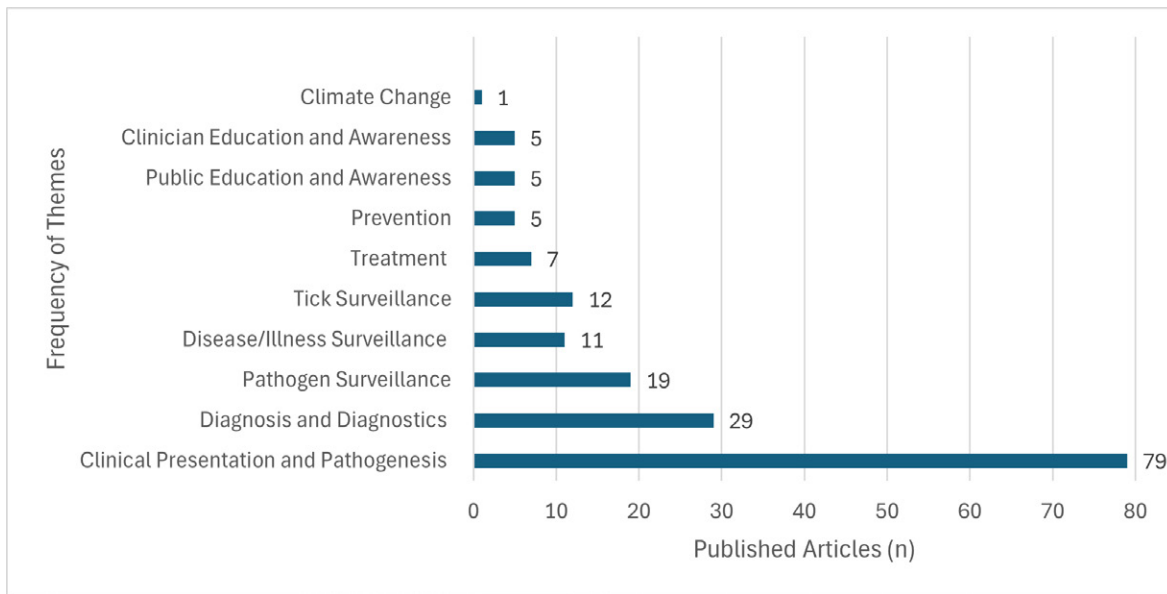
Figure 3. Frequency of themes in literature published from July 1, 2022, to December 31, 2023.

Figure 4 presents the number of publications by tick-associated disease or illness that were captured in the search. Publications related to Lyme disease accounted for the greatest number (>42%) (72/173) of the total number of publications, consistent with the prior scoping review results. The remaining 58% pertains to articles focused on 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 Colorado tick fever. Notably, the results did not capture publications on STARI or tick-borne disease coinfections, including bartonellosis and mycoplasmosis. The disparity between the number of publications on Lyme disease versus other tick-borne diseases underscores the uneven emphasis in current research.

Figure 4. Total number of articles describing tick-borne diseases published from July 1, 2022, to December 31, 2023.

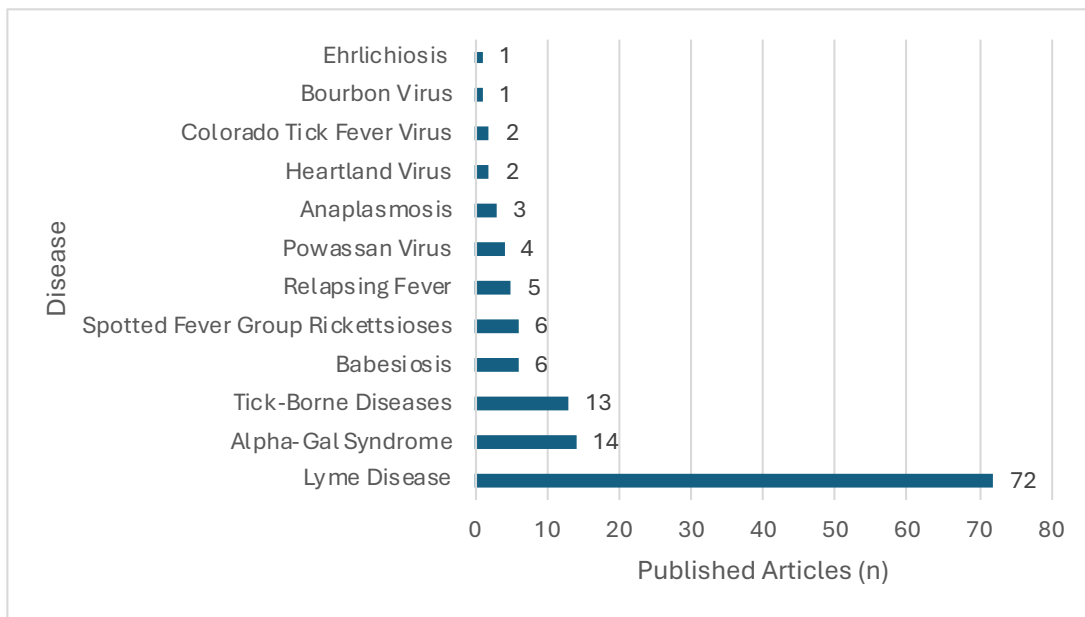Most of the published research was observational or experimental studies (Figure 5). Case studies or case reports accounted for 20% (34/173) of published research, describing Lyme disease (12/34), AGS (6/34), babesiosis (4/34), Powassan virus (3/34), Heartland virus (3/34), tick-borne relapsing fever (3/34), anaplasmosis (2/34), and ehrlichiosis (1/34). No case studies were found that reported on Bourbon virus, Colorado tick fever, ehrlichiosis, spotted fever group rickettsioses, or STARI. Publications reporting on surveys accounted for 8% (13/173) of published research, a notable drop from 43% (139/321) in the previous scoping review. Survey topics included disease surveillance and monitoring programs, disease prevalence surveys, tick-borne diseases and associated illnesses as a general category, education surveys, and tick surveillance.
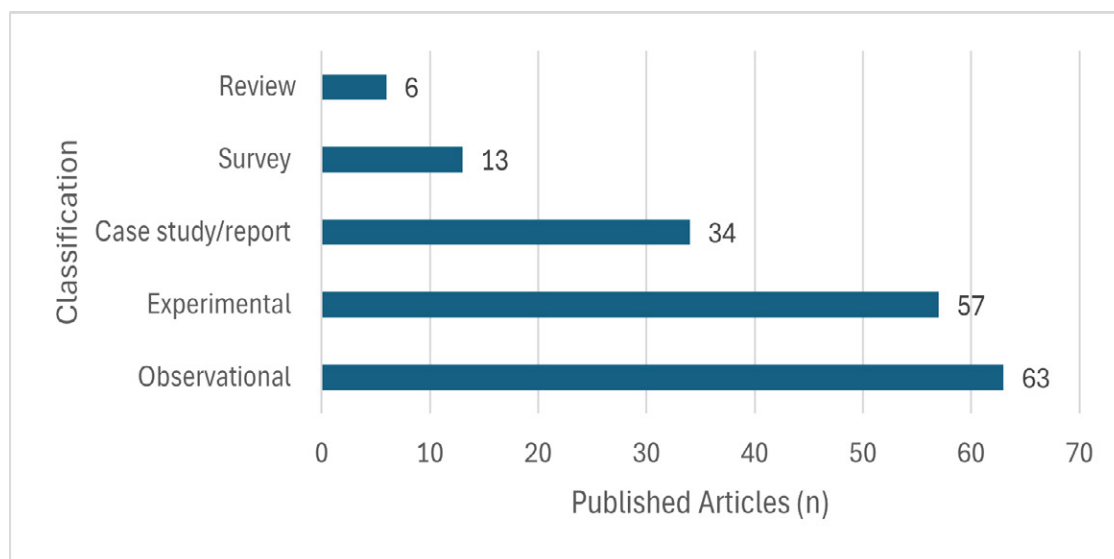

Figure 5. Identified published articles by study design, from July 1, 2022, to December 31, 2023.

Findings: In-Depth Review of Published Literature

This updated review reveals several trends and shifts compared to the initial 2022 review. Publications related to tick-borne diseases and associated illnesses have increased over time, particularly in 2023, marking the highest number of publications to date. This increase underscores a sustained and increasing interest in this research area. The research focus of published literature has also evolved. Whereas the initial review showed a predominant focus on diagnostics and disease surveillance, the updated review indicates a clear shift toward studies focusing on the clinical presentation and pathogenesis of tick-borne diseases and associated illnesses, suggesting the development of a deeper understanding of disease mechanisms and manifestations. Moreover, there is a discernable trend toward observational and experimental studies compared to the predominance of surveys and case studies or reports seen in the earlier review, indicating a move toward more rigorous research methodologies.

While Lyme disease remains a prominent focus across both reviews, research on other tick-borne diseases such as AGS and Colorado tick fever notably increased, showcasing a broader recognition of the importance of studying diverse tick-associated conditions and tick-borne pathogens. These quantitative and qualitative shifts collectively signify an expanding research landscape within the field of tick-borne diseases in the United States, suggesting a more comprehensive approach to tackling these complex public health challenges.

The following sections feature a synthesis, by research theme, of the published research included in this updated review. The goal of these sections is to weave the results of the isolated studies into a constructive "big picture" narrative that can inform future research, policy and funding decisions, as well as programming at the federal, state, territorial, and local levels. Themes with a paucity of research are identified in the concluding discussion section, which also highlights research trends, limitations, and knowledge gaps.

Surveillance

Introduction

During the previous scoping review, from January 1, 2018, to June 30, 2022, 120 articles were published on surveillance: 94 on disease surveillance and 26 on tick surveillance. From July 1, 2022, through December 31, 2023, an additional 40 articles were identified that met the inclusion criteria. Pathogen surveillance was not specifically included in the previous scoping review; however, it was added to this updated review to enable a more complete picture of surveillance efforts in the United States. Notably, pathogen and tick surveillance comprised the majority of surveillance articles scoped for this most recent review (17 and 12 publications, respectively). The articles focused on examining various tick-borne pathogens, their vectors, and the prevalence of infection in different tick species and geographic areas. The remaining articles focused on disease surveillance, encompassing studies on the incidence and distribution of tick-borne diseases, the effectiveness of surveillance methods, and the integration of new technologies and community-based approaches to enhance surveillance accuracy and coverage. This body of literature reflects a growing emphasis on understanding both the ecological dynamics of tick-borne pathogens and the public health impact of the diseases they cause.

Increasing Incidence of Tick-Borne Diseases and Associated Illnesses

The incidence of tick-borne disease cases continues to increase in the United States. According to CDC's Tickborne Disease Surveillance Data Summary, tick-borne diseases are most often reported in specific regions of the United States where ticks thrive. Northeastern states such as Connecticut, Massachusetts, New York, and Pennsylvania, along with the states in the Upper Midwest such as Wisconsin and Michigan, report high incidences of Lyme disease transmitted by blacklegged ticks (*Ixodes scapularis*), also known as deer ticks. Western states such as California and Washington also report Lyme disease cases due to Western black-legged tick bites (*I. pacificus*); and U.S.-Mexico border states report cases of RMSF caused by *R. rickettsii* and transmitted by brown dog ticks (*Rhipicephalus sanguineus*). In the Southeast and Mid-Atlantic regions, states such as Georgia, North Carolina, Maryland, and Delaware report diseases such as ehrlichiosis, transmitted by lone star ticks (*A. americanum*). Although not nationally reportable, AGS is also caused by lone star tick bites and is prevalent where those ticks are found (CDC, 2024a). These patterns vary annually based on climate patterns as well as wildlife activity and life cycles, emphasizing the need for awareness, recognition of symptoms, and tick bite precautions in affected areas (Schotthoefer et al., 2020).

Certain groups are more vulnerable to tick-borne diseases, with heightened risk for outdoor workers, outdoor enthusiasts such as hikers and campers, children and adolescents due to outdoor play, elderly individuals with weakened immunity, pet owners and their pets, and residents of high-tick areas. Additionally, low-income communities and immunocompromised individuals face increased susceptibility. CDC reported that from 2011 to 2022, the annual incidence of reportable tick-borne diseases cases rose by 75%, from 40,795 in 2011 to 71,346 in 2022, estimates that do not account for underreporting (CDC, 2024b). The incidence of reported Lyme disease cases in the United States doubled from 1992 to 1996 and from 2012 to 2016; the increase was especially pronounced among males (Kugeler et al., 2022). A review of Lyme disease surveillance from 2008 to 2020 found that the incidence of Lyme disease cases rose among children (defined as under age 20) in the United States from 2012 to 2017, before returning to baseline from 2017 to 2020 (Shafquat et al., 2023). Lyme disease incidence in children varied greatly across states: states with high reported incidence ranged from 175 to 300 disease cases per 100,000 children per year; states with low reported incidence ranged from 5 to 17 disease cases per 100,000 children per year (Shafquat et al., 2023). Incidence was greatest among children aged 5–9 years (Kugeler et al., 2022; Shafquat et al., 2023).

Several other tick-borne diseases have increased in incidence as well. From 2011 to 2019, reported babesiosis cases (mostly caused by *Babesia microti* in the United States) increased significantly in Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, and Vermont (Swanson et al., 2023). Maine, New Hampshire, and Vermont now have endemic transmission, with reported incidence rising from 9 to 138 cases in Maine, from 13 to 78 in New Hampshire, and from 2 to 34 cases in Vermont (Swanson et al., 2023). From 2010 to 2018, 36,632 rickettsial spotted fever cases were reported to CDC through the National Notifiable Diseases Surveillance System, for an average national incidence of probable and confirmed cases of 12.77 cases per million persons per year (Bishop et al., 2022). Incidence of spotted fever cases increased significantly over this time period, rising from 6 per 100,000 persons in 2010 to

19 per 100,000 persons in 2017 (Bishop et al., 2022). AGS has garnered increased attention in the literature, reflecting heightened awareness of the condition and rising incidence. A CDC analysis found more than 90,000 suspected AGS cases from 2017 to 2021, with the number of new suspected cases increasing by approximately 15,000 each year (J. M. Thompson et al., 2023). In a cohort of 3,000 military recruits reporting for intake to 1 of 10 military bases in the central and eastern United States, the incidence of AGS was 6% (Ailsworth et al., 2024). Military recruits from Arkansas, Oklahoma, and Missouri had the highest incidence (Ailsworth et al., 2024). Rural residence, male sex, and White race were also associated with sensitization, meaning that individuals from these groups were more likely to develop an immune response to the molecule, which can lead to allergic reactions upon subsequent exposures (Ailsworth et al., 2024).

Two notable exceptions to the broad increasing trend in incidence are Colorado tick fever cases, which have declined significantly in recent decades (Padgett et al., 2022) and soft tick relapsing fever (STRF) (Beeson et al., 2023). The decline in Colorado tick fever cases does not seem to be driven by a reduction in infected ticks, as a recent survey by Padgett and colleagues (2022) identified American dog ticks (*Dermacentor variabilis)* that were positive for Colorado tick fever virus in Colorado, Wyoming, and California. The specific reasons for the decrease in case reports remain unclear. They may include a lack of recognition of this disease by health care professionals, insufficient laboratory testing, underreporting to state health departments, or reduced tick exposure. STRF is transmitted to humans by soft-bodied *Ornithodoros* ticks and is a notifiable disease in 12 states. From 2012 to 2021, a total of 251 cases of STRF were reported to CDC; annual incidence did not change significantly over this time period (Beeson et al., 2023). Most of the reported cases (55%) were hospitalized (Beeson et al., 2023).

Lyme Disease Surveillance

Lyme disease has attracted considerable attention in both public health and medical research because of its increasing prevalence and the complexities associated with its diagnosis and treatment. As a tick-borne illness caused by the bacterium *Borrelia burgdorferi*, Lyme disease can lead to a wide range of symptoms, from mild to severe, including chronic neurological and rheumatologic complications if left untreated. This heightened concern is further amplified by the challenges in accurately diagnosing the disease, often because of its varied presentation and the limitations of current diagnostic tools. Consequently, effective methods for estimating the incidence and burden of Lyme disease are crucial for improving public health responses and patient outcomes.

Cocoros and colleagues (2023) assessed the validity of a claims-based algorithm to estimate Lyme disease incidence using an administrative claims database in Massachusetts. The algorithm, which defined cases based on diagnostic code and antimicrobial prescription dispensing within 30 days, identified 12,229 potential Lyme disease cases from 2000 to 2019 (Cocoros et al., 2023). Clinicians reviewed the medical charts from a subset of these cases (n=128). The positive predictive value of algorithm-identified cases for confirmed, probable, or suspected cases was 93.8%, and 66.4% when restricted to confirmed or probable cases (Cocoros et al., 2023). This robust validation of the claims-based algorithm's accuracy underscores its potential as a reliable method for assessing Lyme disease burden. By providing a means to effectively capture and analyze disease trends, such algorithms can offer invaluable insights for informing prevention strategies and policy decisions. Consequently, the findings of Cocoros and colleagues have significant implications for public health surveillance and the development of targeted interventions to mitigate the impact of Lyme disease. The impact of disease burden on health care costs is a critical area of study in the assessment of tick-borne diseases and their socio-economic implications. A study of insurance claims data from a private, employer-based plan in Maryland found that the rate of outpatient visits increased 26% in the 2 years following a Lyme disease diagnosis compared to the 2 years prior (Rebman et al., 2023a). Care utilization increased more among women than men and more among adults than children (Rebman et al., 2023a). These findings reveal the nuanced interplay between disease incidence, health care utilization, and associated costs, providing valuable insights for health care policymakers, insurers, and practitioners alike. Understanding these dynamics is crucial for effective resource allocation, intervention planning, and the delivery of high-quality, cost-effective care in the management of Lyme disease and other similar conditions.

Novel and Emerging Tick-Borne Diseases

Not only have rates of existing tick-borne diseases been increasing, but also new and emerging tick-borne diseases have been reported in the United States. For instance, from 2015 to 2017, a novel *Anaplasma bovis*–like bacterium was identified

in four patients from the Central and Upper Midwest; a genetically identical agent was found in the American dog tick, suggesting this species was the vector (Karpathy et al., 2023). Additionally, a novel *Ehrlichia chaffeensis* genotype was identified in an *A. tenellum* tick, suggesting that *A. tenellum* may serve as an additional vector for *E. chaffeensis* (Arroyave et al., 2022). CDC documented a fatal case of Heartland virus disease, an emerging tick-borne illness spread by lone star ticks in the midwestern and southern U.S. regions, that was acquired in the mid-Atlantic region (Liu et al., 2023). This case signals a potential shift in the geographical distribution of Heartland virus, suggesting an expansion beyond its historically recognized areas. The case also highlights the under-recognition of Heartland virus infection, indicating that cases may be more prevalent than currently reported, especially as tick-borne infections become increasingly common due to factors such as climate change (Bouchard et al., 2019). The authors emphasize the need for expanded testing capabilities to accurately diagnose and manage tick-borne infections, including Heartland virus, in regions where they may not have been previously recognized.

Increasing Tick Geographic Ranges and Seasonal Activity

Several studies documented the geographic expansion of various tick species as well as increases in the duration of tick activity, particularly in the Northeast and Midwest. A tick surveillance study in north-central Oklahoma from 2020 to 2022, found that adult lone star ticks were primarily active 1 month earlier than in historical records, and *Rickettsia* spp., *E. chaffeensis*, *E. ewingii*, and *Borrelia lonestari* were found in 26.4%, 6.1%, 2.5%, and 1.1% of adult lone star ticks, respectively (McClung et al., 2023). A survey found the Gulf Coast tick (*A. maculatum*) in Staten Island and Brooklyn, New York, as well as in Atlantic and Cumberland Counties, New Jersey, indicating increased spread of this species along the northern Atlantic coast (Bajwa et al., 2022). Five out of 10 collected adult Gulf Coast ticks tested positive for *R. parkeri*, the pathogen responsible for *R. parkeri* rickettsiosis (Bajwa et al., 2022). A study of 1,205 nymphal lone star ticks detected Bourbon virus in three ticks, suggesting an emerging new public health threat posed by these ticks in the Northeast (Egizi et al., 2023). From 2008 to 2020, the entomological risk index for anaplasmosis (*Anaplasma phagocytophilum*), which indicates risk for human exposure, **increased in all regions of New York State (Prusinski et al., 2023)**. From 2017 to 2021, tick surveillance in Monmouth County, New Jersey, demonstrated that lone star ticks outnumber blacklegged ticks and found a high degree of variability in nymphal density and infection prevalence, across time and location, and showed an increase in *Borrelia miyamotoi*–infected ticks (Jordan et al., 2022). A survey of ticks in Alaska collected from 2019 to 2020 found established populations of *I. angustus*, *I. uriae*, and *Haemaphysalis leporispalustris* (Hahn et al., 2023). Although the collected ticks did not carry any known human pathogens, they carried *Babesia microti*–like parasites and candidatus *E. khabarensis* (Hahn et al., 2023). In 2021, investigation of two Lyme disease cases in Nebraska revealed a fourth known established population of blacklegged ticks and the first evidence for *B. burgdorferi*–infected blacklegged ticks in the state (Hamik et al., 2023). A review of patients with AGS seen from 2008 to 2018 at Mayo Clinic or the Mayo Clinic Health System identified 47 patients with positive IgE test results for galactose-alpha-1, 3-galactose (alpha-gal). Notably, 11 of these patients resided in states (Alaska, Michigan, Minnesota, and Wisconsin) where the lone star tick had not previously been detected (Chacon Osorio et al., 2022). The authors anticipate a rise in cases of AGS, particularly in regions where lone star tick populations are spreading. They highlight the expanding distribution of the lone star tick, now increasingly documented across the southeastern, northeastern, and central regions of the United States.

Despite the increase in tick ranges, considerable diversity persists throughout the United States in tick abundance and the prevalence of tick infections. Since 2002, 30 of the 41 states where vector ticks are considered established have reported detection of at least one of the seven pathogens transmitted by blacklegged ticks and western blacklegged ticks: *B. burgdorferi, Borrelia mayonii, Borrelia miyamotoi, A. phagocytophilum, E. muris eauclairensis, Babesia microti*, and Powassan virus (Fleshman et al., 2022). A survey of the diversity of outer surface protein C (OspC) genetic alleles in *B. burgdorferi*–infected black-legged ticks in Delaware similarly revealed pathogen diversity by state region (Shifflett et al., 2023). The OspC gene of *B. burgdorferi* exhibits substantial genetic variation across the pathogen's distribution; only a subset of known OspC variants cause infections in humans. Strains containing 15 previously characterized OspC alleles accounted for nearly all tick infections in the Delaware survey, and 40% of ticks had mixed strain infections (Shifflett et al., 2023).

Tick Surveillance Methodology

Several studies evaluated the reliability and accuracy of current and emerging tick surveillance methods. To assess the concordance between passive and active tick surveillance, Holcomb and colleagues (2023) analyzed tick surveillance

data collected in Connecticut from 2019 to 2021. They found high concordance between active and passive surveillance estimates for tick and pathogen presence and pathogen prevalence but little to no concordance for tick abundance estimates (Holcomb et al., 2023). Variation in data collection can preclude accurate determination of tick abundance and longer-term population trajectories. A moving window analysis of 289 datasets on blacklegged tick abundance from seven U.S. locations found that all the datasets required 4 or more years before reaching stability (Christie et al., 2022). Datasets collected via dragging reached stability significantly faster than those collected via opportunistic sampling, as did datasets that sampled nymphs or adults rather than larvae (Christie et al., 2022).

Several studies investigated how community-submitted samples and reports of tick-borne disease might be used to enhance surveillance. As part of a statewide citizen science survey conducted during 2021, Missourians submitted 12,819 ticks, the majority of which were lone star ticks (Hudman & Combes, 2023). This low-cost approach to surveillance may facilitate determination of statewide trends in tick abundance. However, analysis of tick submissions from 2015 to 2019 to a passive surveillance testing service in Massachusetts found that counties with higher levels of education attainment submitted more ticks. These findings suggest that passive surveillance data may fail to reflect tick abundance in underserved areas and caution against relying solely on passive surveillance. The disparities in tick submissions based on education levels highlight the importance of comprehensive public education and engagement initiatives to ensure equitable participation in tick surveillance efforts. Furthermore, such initiatives could address the need for targeted awareness campaigns aimed at different demographic groups to effectively communicate the risks associated with tick exposure and the importance of preventive measures throughout the year, including strategies to minimize tick encounters in both outdoor and indoor environments. Another study examined the value of integrating a web survey on tick bite encounters and tick-borne diseases with CDC data on disease incidence, tick abundance data, and canine serological data (Maxwell et al., 2023). This integrated approach could provide a more comprehensive understanding of tick-borne disease dynamics and help inform public health interventions.

Other studies developed and assessed novel methods for conducting and facilitating tick surveillance. Burtis and colleagues (2022) generated and validated a habitat suitability map for determining where blacklegged ticks are established and where *B. burgdorferi*–infected blacklegged ticks are likely to occur (Burtis et al., 2022). They then identified counties where infected blacklegged tick populations may be expanding, which could help identify regions to target in future tick surveillance efforts (Burtis et al., 2022). Bhadra and colleagues (2023) developed novel arthropod- and pathogen-specific assays for blacklegged ticks and *B. burgdorferi*, respectively, that couple two multiplex loop-mediated isothermal amplification (LAMP) reactions with oligonucleotide strand displacement probes. These assays can use macerated tick samples collected in the field with no sample preparation (Bhadra et al., 2023). In field conditions, the assays demonstrated 97–100% sensitivity and 100% specificity (Bhadra et al., 2023).

Factors Influencing Risk for Tick Bites and Disease Transmission

Several studies analyzed factors involved in the risk of receiving a tick bite from an infected tick and disease transmission risk. An analysis of the blood meals of nymphs and adult blacklegged ticks collected from five field sites in New England found that ticks that fed on shrews or mice as larvae were more likely to become infected with *B. burgdorferi* (Goethert et al., 2023). A study of tick saliva found great variability in the amount of alpha-gal in lone star tick saliva, with generally higher amounts found in ticks fed primarily on human blood (Maldonado-Ruiz et al., 2023). These findings suggest that host-specific genetic components affect the production of alpha-gal in tick saliva and may contribute to variability in the development of AGS. Drag sampling conducted in Minnesota from 2015 to 2017 found that adult ticks were active from April through November, whereas nymphs were most active from May through August, with peak activity in June (Burtis et al., 2023). The observed period of peak nymphal activity corresponded to the typical Upper Midwest seasonal peak in human Lyme disease cases (Burtis et al.,2023). A 2019 survey of three public parks on Staten Island, New York, conducted from May to August found that nymphal densities for three tick species (blacklegged, lone star, and Asian longhorned [*H. longicornis*]) were highest on unmaintained herbaceous habitats and trails (Hassett et al., 2022). An analysis of urban yards in Staten Island, New York, found that greater canopy cover and the presence of log or brush piles increased the likelihood of the presence of one or more of three tick species (blacklegged, lone star, and Asian longhorned), whereas fencing reduced the likelihood (Gregory et al., 2022). However, a study of residential properties in Dutchess County, New York, a high-incidence area for Lyme disease, found no consistent associations between amount of forest or forest

fragmentation and residential tick abundance (Keesing et al., 2023). Tick abundance varied consistently by neighborhoods and within small areas (~1 hectare) within neighborhoods (Keesing et al., 2023).

Conclusion

The increasing incidence of tick-borne diseases in the United States underscores the growing public health challenge posed by these pathogens. More specifically, the persistent increase in cases of AGS and diseases such as Lyme disease, babesiosis, and rickettsial spotted fever, as well as the emergence of novel pathogens such as Heartland virus, Powassan virus, and Bourbon virus, highlight the dynamic nature of tick-borne disease epidemiology. These trends reflect broader ecological changes, including shifts in tick populations and activity patterns influenced by climate change and human behaviors.

Incidence was greatest among children aged 5–9 years, indicating that this demographic is particularly vulnerable to tick-borne diseases. This heightened vulnerability may be attributed to several factors. Children in this age group tend to spend significant time outdoors, particularly in grassy, wooded, or shrubby areas where ticks thrive. Furthermore, young children may not fully comprehend the risks associated with ticks, leading to a lack of precautionary measures such as avoiding high grass or wearing protective clothing, and they are less likely to check themselves for ticks after outdoor play.

Surveillance programs can monitor tick populations and the prevalence of tick-borne pathogens, providing valuable data to predict and respond to disease outbreaks. Implementing integrated pest management strategies, including habitat modification and tick control measures, can reduce tick populations in public spaces and residential areas. Additionally, collaboration between public health agencies, health care providers, and communities is essential to enhance early diagnosis, treatment, and reporting of tick-borne diseases, ultimately reducing their impact on children's health.

This updated review reflects a notable focus on pathogen surveillance, including the examination of tick-borne pathogens, vectors, and the prevalence of infection across different regions. The present body of literature on tick-borne disease surveillance provides critical insights into the patterns and drivers of disease incidence. Continued investment in surveillance, public education, and research is essential to mitigate the impact of tick-borne diseases and enhance public health preparedness. By leveraging advanced surveillance technologies and community engagement, we can improve our understanding of tick-borne disease dynamics and develop more effective interventions to protect at-risk populations.

Diagnosis and Diagnostics

Introduction

During the period of the previous scoping review, from January 1, 2018, to June 30, 2022, 40 articles on diagnosis and diagnostics were published. From July 1, 2022, to December 31, 2023, an additional 28 articles on diagnosis and diagnostics were published. The majority of these articles (18/28) focused on the difficulties involved in diagnosing early Lyme disease and potential improvements to the standard serological tests, which have low sensitivity for detecting early infection. The remaining articles focused on developing better diagnostic tools for tick-borne diseases that are rising in prevalence in the United States, such as babesiosis, RMSF, and anaplasmosis.

Lyme Disease

Accuracy of Current Diagnostic Approaches

Early symptoms of Lyme disease may include erythema migrans (EM). However, diagnosis is complicated by only 60–70% of patients presenting with EM, and less than 35% presenting with the classic bull's eye rash (Marques, 2010; Steere et al., 1987). In the absence of an EM rash, a Lyme disease diagnosis requires positive two-tier serologic testing (standard or modified), which takes several days after an infection to yield results. Clinicians, therefore, must make treatment decisions prior to receiving the test results (Garro et al., 2022). At eight emergency departments participating in Pedi Lyme Net, the pediatric Lyme disease research network at Boston Children's Hospital, 13.9% of children who tested positive for Lyme disease using the standard two-tier Lyme disease test were not initially treated with an appropriate antibiotic, and 13.3% without Lyme disease received potentially unnecessary antibiotics (Garro et al., 2022). In a sample

of 192 children with an EM lesion, two-tier Lyme disease serology had higher sensitivity in children with multiple lesions (76.8%) compared to those with a single lesion (38.1%) (A. D. Thompson et al., 2023).

Compared to patients who noted viral-like symptoms as the first manifestation of Lyme disease, patients who detected the EM rash first experienced a shorter duration of illness (5 days versus 6.2 days) and were more likely to have seen or removed a tick and to be non-Hispanic white (Rebman, et al., 2023b). EM-first patients had a 22% decrease in time to treatment compared to symptoms-first patients (Rebman et al., 2023b). Consistent with prior research, racial differences were found in a study conducted at an academic medical center in suburban Maryland: Black patients with Lyme disease were more likely to present with disseminated disease symptoms; and among patients presenting with an EM rash, Black patients experienced significantly longer times to appropriate antibiotic treatment compared to other patients (Starke et al., 2023). Similar racial differences were seen in a study of Lyme disease diagnoses among children seen at the eight emergency departments participating in the Pedi Lyme Net clinical research network from June 2015 to August 2022. Compared to children of other racial backgrounds, Black children were less likely to receive a Lyme disease diagnosis at an emergency department; less likely to be diagnoses with cutaneous manifestations of Lyme disease; and more likely to be diagnosed with a swollen joint indicative of Lyme disease arthritis (Hunt et al., 2023). Together, these findings emphasize the need for improved education and guidelines for clinicians regarding Lyme disease presentation and diagnosis in individuals with darker skin tones.

Novel Potential Diagnostic Approaches

In 1995, CDC recommended using a standard two-tier serologic assay (CDC, 1995). In 2019, CDC updated serology testing guidelines for Lyme disease diagnosis to include alternative modified two-tier testing, in which the western blots of standard testing are replaced by an additional enzyme-linked immunosorbent assay (ELISA) (Mead et al., 2019). Both methods rely upon antibody capture, which has limited ability to detect early Lyme disease. Moreover, not all patients seroconvert (Lantos et al., 2021). These methods also complicate the determination of recovery from acute infection and the detection of reinfections, as antibodies typically remain elevated following the resolution of acute infections.

Several studies compared the performance of the standard and modified two-tier testing and evaluated further modifications to these approaches. Sabin and colleagues (2022) compared the results of samples from 320 patients with suspected Lyme disease, tested using the standard two-tier method and the modified two-tier algorithm. Modified testing confirmed illness in all patients who were positive by standard testing and in 30 patients who were negative by standard testing (Sabin et al., 2023). Modified testing displayed greater sensitivity to early infections, but was insufficiently sensitive to identify other *Borrelia* infections (Sabin et al., 2023). Routine adoption of modified testing could improve testing sensitivity for early Lyme disease caused by *B. burgdorferi* but may not detect illness caused by *Borrelia mayonii* and *Borrelia miyamotoi* (Sabin et al., 2023). When testing a CDC panel of 92 samples, Pratt and colleagues (2022a) found that using a novel lab-developed antibody-capture immunoassay increased sensitivity but decreased specificity compared to modified two-tier testing and the standard two-tier algorithm, which did not significantly differ from one another (Pratt et al., 2022a). Lee-Lewandrowski and colleagues (2023) found high agreement (98%) between the Sofia Lyme assay— a rapid lateral-flow method that can be performed in real time—and the Zeus ELISA Borrelia VlsE1/pepC10 IgG/IgM test, which is used in the Food and Drug Administration (FDA)-approved modified two-tier test. Finally, a series of retrospective analyses found that the addition of whole blood real-time polymerase chain reaction (WB-RTPCR) to antibody capture methods identified an additional 8–10% of positive specimens (an additional 131 out of 1,379 positive specimens, and 31 out of 358 samples; Pratt et al., 2022b) .

Several studies investigated novel alternative methods for detecting early *B. burgdorferi* infections. Antigen-based blood tests for Lyme disease are not currently available. S. Kim and colleagues (2023) showed that a portable smartphone-based fluorescence microscope that measures immunoagglutination on a paper microfluidic chip can detect three *B. burgdorferi* antigens, OspA, OspC, and VlsE (S. Kim et al., 2023). Detection of the latter two antigens may aid in determining Lyme disease stage (S. Kim et al., 2023). PCR is not reliable for detecting *B. burgdorferi* in blood, urine, or cerebrospinal fluid because of generally low pathogen levels in these fluids. Given that skin is the initial site of replication of *B. burgdorferi,* Kight and colleagues (2022) developed and tested a microneedle device that can safely, affordably, and painlessly sample interstitial fluid that is tested for the presence of spirochetes via PCR (Kight et al., 2022). When tested on porcine ear skin, the device had an approximately 80% detection rate (Kight et al., 2022). Finally, Haddad and colleagues (2023) showed that using medium enriched for newly synthesized antibodies (MENSA), a novel diagnostic fluid containing

antibodies produced in vitro by circulating antibody-secreting cells, detected early Lyme disease in 8 out of 12 patients. MENSA antibodies decline to baseline 40 days after successful treatment, whereas serum antibodies remain elevated for at least 80 days, suggesting that MENSA antibodies may serve as an indicator of treatment success and perhaps enable detection of repeat infections.

Additional studies examined gene expression, proteomics, and other potential correlates of Lyme disease that may improve diagnosis. RNA sequencing to analyze gene expression in the peripheral blood mononuclear cells (PBMCs) of patients with post-treatment Lyme disease, acute Lyme disease, and healthy controls revealed a unique mRNA biomarker set that can distinguish individuals with acute and post-infection Lyme disease from healthy individuals (D. Clarke et al., 2022). This gene expression data could help elucidate disease mechanisms and improve diagnosis. Boada and colleagues (2022) analyzed the serum proteomes from 23 study participants during acute infections and convalescence from Lyme disease and West Nile virus, using a depletion-based high-throughput shotgun proteomics pipeline (dHSP) as well as a non-depleting blotting-based low-throughput platform (MStern). Integrated analyses were then used to identify shared host proteome responses, differentially abundant proteins for the two infections, and proteins that distinguished localized from disseminated Lyme disease. Finally, in a health system cohort of more than 1 million individuals, increasing blood cholesterol levels and genetic risks for high cholesterol were associated with increased risk for Lyme disease and increased elevations in cholesterol following diagnosis (Forrest et al., 2023). *B. burgdorferi* cannot synthesize cholesterol, but instead acquires it from its host, and research in animals suggests that hypercholesteremia can increase disease severity. Forrest and colleagues' (2023) findings suggest that high cholesterol levels in humans may similarly increase susceptibility and disease severity.

Other Tick Borne-Diseases

New and emerging diagnostic techniques may contribute to apparent increases in infection rates by enabling the detection of previously missed infections. In 2020, Montana reported a large increase in Colorado tick fever cases (Soto et al., 2023). The increase appears to have been driven by a change in state testing practices (Soto et al., 2023). Prior to 2020, Montana relied on serological testing for Colorado tick fever; from 2011 to 2019, an average of 1.3% of specimens tested positive (Soto et al., 2023). In 2020, because of COVID-19 testing needs, state laboratories began sending specimens to CDC, which tests for Colorado tick fever using reverse transcription PCR (RT-PCR) for acute specimens and plaque-reduction neutralization test (PRNT) for convalescent specimens. Approximately 21% and 5.7% of specimens tested positive via RT-PCR and PRNT tests, respectively (Soto et al., 2023). This shift to more sensitive diagnostic methods significantly increased the detection of infections that were previously missed, providing a more accurate picture of the disease's prevalence. The dramatic rise in reported cases reflects improved diagnostic capabilities rather than a true surge in infections. Understanding this distinction is crucial for accurately assessing disease burden, guiding public health responses, and informing resource allocation. Improved diagnostics can help in more effectively managing public health strategies and ensuring that interventions are appropriately targeted based on the true extent of the disease.

Testing for RMSF remains a challenge. Of 170 patients under age 21 who were tested for RMSF in the Stonybrook Medical System in Suffolk, New York, from 2010 to 2020, only 5.8% met CDC criteria for rickettsial infection. Clinicians may need additional guidance regarding when diagnostic testing for RMSF is appropriate. Many of the tested patients lacked the classic symptoms of RMSF, such as fever (Wang & Handel, 2023). Some reference labs cultivate spotted fever group *Rickettsia* (SPFG) to augment diagnosis. However, current isolation methods for SPFG require sample volumes of greater than 1 mL. Condit and colleagues (2022) developed and validated a novel small-volume cell culture method that reduced sample requirements to 50 µL of serum, unprocessed whole blood, or plasma (Condit et al., 2022).

Other studies have explored techniques to improve testing for other tick-borne diseases increasing in prevalence in the United States. Stellrecht and colleagues (2022) adapted two multiplex real-time PCR tests—one for *A. phagocytophilum* and *E. chaffeensis,* and a second for *Babesia microti*—to the Panther Fusion system, an advanced, fully automated molecular diagnostic platform (Stellrecht et al., 2022). The tests showed comparable performance to manual PCR tests for these pathogens and may help meet the increased demand for tick-borne disease testing. Tagliafierro and colleagues (2022) employed a peptide array to select three optimal peptides for serologic diagnosis of past infections with *A. phagocytophilum* and *Babesia microti* (Tagliafierro et al., 2022). Gagnon and colleagues (2022) developed a monoclonal antibody-based BmGPI12 capture assay that uses a combination of two monoclonal antibodies, 4C8 and

1E11, to detect active *Babesia microti* infection. The capture assay had a 97% correlation with RNA-based PCR, suggesting the assay might be used alone or in combination with PCR to detect active *Babesia microti* infection (Gagnon et al., 2022). In Alabama, a *Borrelia lonestari* infection was identified using PCR, sequencing, and phylogenetic analysis in an immunocompromised patient with relapsing fevers (Vazquez Guillamet et al., 2023). These infections are infrequently reported. The apparent low incidence of infections caused by this subspecies may result from underdiagnosis or from it having less pathogenic potential in humans. *Borrelia lonestari* is difficult to isolate via classic laboratory methods such as culturing (Barbour et al., 1996; Varela et al., 2004).

Conclusion

Diagnosis of early Lyme disease continues to be challenging because of the low sensitivity of current serological and clinical diagnostic methods. The variability in clinical presentation, with a significant proportion of cases lacking the classic EM rash, coupled with difficulties in detecting rashes on darker skin tones, contributes to racial and ethnic disparities in treatment onset and disease severity. These issues underscore the urgent need for enhanced clinician awareness of these issues and more accurate and accessible point-of-care diagnostics for Lyme disease.

Beyond Lyme disease, the landscape of tick-borne diseases is evolving, with rising case numbers of illnesses such as babesiosis, RMSF, and anaplasmosis. Advances in diagnostic technology, including multiplex PCR tests, antigen-based detection methods, and innovative approaches such as microneedle devices, offer promising solutions for these emerging challenges. The increased detection rates of underreported diseases, such as Colorado tick fever and *Borrelia lonestari*, underscore the impact of improved diagnostics on our understanding of disease prevalence.

While these diagnostics advancements are promising, further validation, market investment, and widespread adoption are necessary to ensure that they are effective and accessible. Continued research and development will be crucial in enhancing diagnostic accuracy for both Lyme disease and other tick-borne diseases, ultimately improving patient outcomes and informing public health strategies.

Clinical Presentation and Pathogenesis

Introduction

During the initial scoping review from January 1, 2018, to June 30, 2022, 14 articles were published that explored clinical presentation and pathogenesis. Subsequently, between July 1, 2022, and December 31, 2023, an additional 76 articles contributed significantly to these topics, a notable increase from the earlier review. The current publications identified cover a range of specific diseases such as Lyme disease and AGS, as well as various factors affecting clinical presentation and pathogenesis, for example infecting pathogens and host responses. The remaining articles focused on investigating pathophysiological mechanisms linked to tick-borne diseases and associated conditions, including immune responses, microbial interactions, and genetic factors.

Lyme Disease

Lyme disease, caused by the spirochete *B. burgdorferi*, illustrates the complex nature of tick-borne diseases and associated illnesses. The progression of Lyme disease can vary widely among individuals, with some presenting a distinctive EM rash and others facing complications affecting the nervous, cardiac, or musculoskeletal systems (A. D. Thompson et al., 2023). The variability in disease expression, manifestation, and recovery from the acute phase following treatment underscores the importance of considering individual factors such as immune response, genetic predispositions, and environmental influences.

Deciphering the Genomic Diversity of Borrelia burgdorferi: Implications for Disease Presentation

Whole genome sequencing, encompassing isolates from diverse geographic regions, helps to reveal the genomic landscape of *B. burgdorferi*. A comprehensive classification system, integrating plasmid profiles and surface lipoproteome annotations, demonstrates the existence of a core genome and a set of strain-variable elements (Lemieux et al., 2023). The core genome comprises genetic elements essential for *B. burgdorferi*'s survival across different strains, while the

strain-variable elements, particularly those that encode surface-exposed lipoproteins, contribute to genetic diversity and the adaptability of the bacterium (Shifflett et al., 2023). Within these variable elements, strain-specific clusters are implicated in the diverse clinical presentations observed across *B. burgdorferi* strains, influencing the severity and progression of infections in individuals. Additionally, the presence of strain-variable elements suggests a mechanism for the bacterium's adaptability and potential dissemination within the host organism, emphasizing their role in the evolutionary and pathogenic dynamics of *B. burgdorferi*. Understanding of this genomic complexity can inform diagnostic approaches and therapeutic strategies, and provide insights into the host-pathogen interactions of Lyme disease.

MicroRNA Interactions and Ribosomal Structural Studies

Molecular research aimed at understanding early Lyme disease pathogenesis has revealed intricate interactions between *B. burgdorferi* and host cells. Specifically, investigations into microRNA responses to *B. burgdorferi* within human dermal fibroblasts highlight miR146a-5p as a significant upstream regulator influencing the immune response (Victoria et al., 2023). Furthermore, the structural characterization of *B. burgdorferi*'s ribosome, achieved through cryo-electron microscopy (Cryo-EM), represents a milestone in understanding the molecular mechanisms involved in the life cycle and function of *B. burgdorferi* (M. R. Sharma et al., 2023). This structural insight not only aids in understanding the ribosomal targeting of antibiotics but also opens avenues for novel treatment design and therapeutic strategies against Lyme disease.

Genetic Manipulation of Borrelia burgdorferi for Enhanced Research and Therapeutic Development

In the context of the genetic manipulation of *B. burgdorferi*, challenges associated with the conventional method of electroporation have prompted the exploration of alternative means. Bacteriophage-mediated transduction may serve as a potential complement to electroporation, offering a novel avenue for introducing foreign DNA into *B. burgdorferi* (Eggers, 2022). The use of the borrelial phage φBB-1 showcases the feasibility of transducing DNA between spirochetes of different genetic backgrounds, providing a valuable addition to the toolkit for genetic manipulation of the Lyme disease spirochete. This advancement enables a more complete examination of the *B. burgdorferi* genetic landscape, enhancing the understanding of intricate interactions between *B. burgdorferi* and its host and establishing the foundation for strategic disease interventions. Exploring genetic elements linked to antibiotic resistance not only steers the development of more effective treatment strategies but also addresses the evolving challenges of drug resistance. Moreover, the identification of genetic variations among strains streamlines the development of advanced diagnostics, promoting early detection and timely intervention.

Molecular Mechanisms of Lyme Neuroborreliosis

Investigations into the factors facilitating the transmigration of *B. burgdorferi* across the blood–brain barrier illuminate the intricacies of Lyme neuroborreliosis, a condition marked by the invasion of the nervous system by the bacterium. The Rrp2-RpoN-RpoS pathway emerges as a pivotal determinant in *B. burgdorferi*'s ability to transmigrate across the blood–brain barrier (Alanazi et al., 2023). This regulatory cascade involves the response regulator protein Rrp2, the sigma factor RpoN, and the sigma factor RpoS, collectively influencing gene expression and bacterial adaptation. Additionally, a major surface lipoprotein, OspC, is identified as a significant contributor to this transmigration process, providing a specific molecular target for exploration (Alanazi et al., 2023). Thus, OspC, a key player in the early stages of infection, facilitates the interaction between *B. burgdorferi* and the host (Castro-Padovani et al., 2023; Rudolph et al., 2023). This comprehensive understanding of neuroinvasion by *B. burgdorferi* reveals potential targets for therapeutic interventions. By elucidating the roles of the Rrp2-RpoN-RpoS pathway and OspC, researchers gain insights that may guide the development of targeted strategies aimed at disrupting or inhibiting these specific molecular mechanisms, offering promising prospects for improved therapeutic interventions in Lyme neuroborreliosis.

Insights from Clinical Observations and Advanced Imaging

Using optical coherence tomography (OCT), Padula & Sayyed (2023) have identified peripapillary ischemia as a potential biomarker for Lyme disease. The researchers' focus on peripapillary ischemia suggests the *B. burgdorferi* spirochete's ability to induce vascular and circulatory changes, emphasizing the optic nerve's sensitivity to blood flow alterations as a key consideration in Lyme disease clinical presentation. This approach holds promise for enhancing clinicians' understanding of ocular involvement in Lyme disease, providing valuable insights into the pathophysiology of the disease and enabling the detection of structural changes and abnormalities that contribute to the wide range of symptoms in Lyme disease

patients. Moreover, the integration of OCT into Lyme disease diagnostics represents a step forward in personalized medicine, where tailored treatment approaches can be developed based on individual disease manifestations. By combining clinical observations with advanced imaging techniques, health care providers can better assess disease severity, monitor treatment response, and identify potential complications earlier in the disease course.

Post-Treatment Lyme Disease

Post-treatment Lyme disease research focuses on understanding the persistence of symptoms and long-term consequences after standard antibiotic treatment (D. J. B. Clarke et al., 2022; Kanjana et al., 2023; Marvel et al., 2022). Despite treatment, some individuals continue to experience symptoms, leading to post-treatment Lyme disease syndrome (PTLDS) (Chung et al., 2023). This syndrome encompasses persistent symptoms such as fatigue, musculoskeletal pain, and cognitive difficulties beyond the initial treatment phase. Ongoing research aims to unravel the underlying mechanisms contributing to these persistent symptoms. Factors such as immune response, bacterial persistence, and potential coinfections are being investigated to understand the complex presentation of Lyme disease. Notably, neurological manifestations, including cognitive difficulties, can persist even after the *B. burgdorferi* spirochete's clearance, making it a significant concern (Hernández et al., 2023).

To dissect these complexities, longitudinal studies, employing advanced neuroimaging techniques such as functional magnetic resonance imaging (MRI), are instrumental in comprehending the impact of Lyme disease on the central nervous system and cognitive function post-treatment (Marvel et al., 2022). Research delves into the role of the immune system in post-treatment symptoms, exploring immune dysregulation, persistent inflammation, and the role of microRNAs. To track symptom trajectories, extended follow-up periods in longitudinal studies are deemed essential (Chung et al., 2023). These studies aim to characterize clinical outcomes and quality of life in patients with persistent symptoms, shedding light on the long-term impact of Lyme disease on various organ systems.

Tick-Borne Viruses

Tick-borne viruses introduce an additional layer of complexity to the tick-borne disease clinical landscape. Powassan virus, transmitted by blacklegged ticks, shares its vector with *B. burgdorferi*, the causative agent of Lyme disease. The presence of both pathogens in blacklegged ticks can aid Powassan virus replication through mechanisms such as immunomodulation, enhanced vector competence, resource competition, and potential effects on vector lifespan and behavior (Hart et al., 2022). Recent research highlights the severity of Powassan virus infections, with high mortality rates and significant long-term neurological sequelae in survivors. These infections can result in persistent symptoms such as cognitive deficits, speech difficulties, and motor impairments, which significantly impact quality of life (Farrington et al., 2023). The neuroinvasive nature of Powassan virus often leads to a range of neurological manifestations, including encephalitis and myelitis, complicating the clinical picture and underscoring the need for a comprehensive understanding of its long-term effects (Johnson et al., 2022; Kakoullis et al., 2022).

Similarly, a case of Heartland virus reported by Ahlers and colleagues (2022) highlights the potential for severe manifestations associated with tick-borne viral infections beyond the more commonly known symptoms. The authors documented a case of secondary hemophagocytic lymphohistiocytosis (HLH), a rare yet severe complication of Heartland virus infection (Ahlers et al., 2022). HLH is a hyperinflammatory syndrome characterized by uncontrolled activation of immune cells, leading to organ damage and systemic illness. The complex interplay between host immune responses and emerging pathogens such as Heartland virus underscores the importance of continued surveillance and research into tick-borne diseases (Liu et al., 2023). Understanding the full spectrum of disease presentation, including rare complications such as HLH, is crucial for timely diagnosis, management, and prevention strategies in regions where these viruses are endemic.

Alpha-Gal Syndrome

AGS, characterized by IgE-mediated hypersensitivity to alpha-gal, introduces a unique dimension to tick-associated illnesses (Kersh et al., 2023). This condition has been increasingly recognized for its diverse clinical manifestations, and a noteworthy case has brought attention to the potential for chronic periorbital edema as an unusual presentation of AGS (Avila & Wojno, 2022). Moreover, the impact of AGS appears to differ across age groups. For example, AGS predominantly

manifests as isolated gastrointestinal symptoms in the pediatric population (Busing et al., 2023; Glynn et al., 2023). These observations demonstrate the variability in symptom presentation and underscore the importance of adopting a comprehensive, tailored approach to both diagnosis and management of AGS.

Conclusion

Despite the remarkable progress in understanding tick-borne diseases, critical knowledge gaps persist in our understanding of both pathogenesis and clinical presentation. The complex dynamics of host-pathogen interactions, particularly the role of tick saliva components and host genetic susceptibility, remain areas of ongoing investigation (Maldonado-Ruiz et al., 2023). Research aimed at unraveling the molecular intricacies of how these pathogens manipulate the human immune system and establish infection continues to be a focal point across various disciplines (Beri et al., 2023; Dominguez et al., 2022; Kondethimmanahalli & Ganta, 2022; A. K. Sharma et al., 2023).

Tick-borne diseases and associated illnesses are often characterized by complex clinical presentations, with a diverse array of symptoms ranging from mild to severe, often exhibiting atypical manifestations that can mimic other illnesses. The elusive nature of these diseases and the potential for coinfections complicate accurate diagnosis and treatment. Persistent symptoms associated with Lyme disease, in particular, spark debate within the medical community, as some patients report ongoing symptoms post-treatment, necessitating a more thorough evaluation of the disease's long-term implications.

Addressing these knowledge gaps remains a priority through ongoing multidisciplinary collaborations. The integration of research on tick saliva, pathogenesis, and clinical presentation is vital for a holistic approach to addressing tick-borne diseases and associated illnesses. These concerted efforts hold the promise of not only advancing scientific understanding, but also improving the lives of those affected by these intricate and often misunderstood diseases.

Treatment

Introduction

During the initial scoping review from January 1, 2018, to June 30, 2022, 9 articles were published that explored the treatment of tick-borne diseases. Subsequently, between July 1, 2022, and December 31, 2023, an additional 10 articles contributed to these topics. Recent studies have evaluated the safety and efficacy of antibiotics such as doxycycline in young children with Lyme disease, investigated potential targets for narrow-spectrum antibiotics against *B. burgdorferi*, and assessed the impact of the COVID-19 pandemic on the treatment of spotted fever group rickettsioses and ehrlichiosis. Other research has focused on the pathophysiological mechanisms linked to tick-borne diseases, such as the disruption of endothelial cell integrity by *R. parkeri* and potential therapeutic interventions.

Lyme Disease Treatments

The treatment of tick-borne diseases remains a critical area of medical research because of the prevalence and severity of these infections. Recent studies have focused on improving the therapeutic strategies for diseases such as Lyme disease and spotted fever group rickettsioses, addressing both the effectiveness and safety of current treatments, as well as exploring novel therapeutic targets and interventions.

Concerns regarding permanent tooth staining from doxycycline have hindered its use in children under age 8 years. Brown and colleagues (2023) performed a retrospective analysis of 32 children under age 8 who received doxycycline for Lyme disease. Parents of 18 of these children responded to a post-treatment follow-up survey; none reported treatment failure, but 2 reported dental staining (Brown et al., 2023). These findings suggest that while alternative antibiotics such as amoxicillin remain the preferred treatment for Lyme disease in young children, doxycycline is a safe and effective alternative.

Current treatment of *B. burgdorferi* requires long courses of broad-spectrum antibiotics, which has side effects and may increase antibiotic resistance. Gwynne and colleagues (2023) developed an in-silico model of *B. burgdorferi* metabolism to identify potential targets for narrow-spectrum antibiotics. Model predictions were validated by testing several

small-molecule enzyme inhibitors, several of which had specific activity against *B. burgdorferi* and, although unsuitable for clinical use, may serve as lead compounds for drug development (Gwynne et al., 2023).

Treatment for Rickettsiosis

The COVID-19 pandemic has significantly impacted health care systems worldwide, affecting the diagnosis and treatment of various diseases. In the context of tick-borne diseases, delays in diagnosis and treatment can lead to worsened patient outcomes. Arahirwa (2023) examined these delays in the diagnosis and treatment of rickettsial infections before and during the COVID-19 pandemic (March 2020–February 2021) among 240 patients who were diagnosed with a spotted fever group rickettsiosis or ehrlichiosis and received a positive *R. rickettsii* or *Ehrlichia* indirect immunofluorescence assay immunoglobulin G antibody test result (Arahirwa et al., 2023). The median time from presentation to diagnosis during the COVID pandemic period was longer (5 days) than pre-COVID (1 day; Arahirwa et al., 2023). During the pandemic, patients were more likely to use telemedicine services and to experience delays in treatment, and less likely to utilize emergency departments (Arahirwa et al., 2023).

Spotted fever group pathogens infect and proliferate in host vascular endothelial cells, ultimately impairing vascular endothelium barrier functions. Y. Kim and colleagues (2023) assessed the impact of *R. parkeri* infection in an in vitro model of transformed brain microvascular endothelial cells. Continuous monitoring of transendothelial electric resistance across the cell monolayer revealed a decrease in electric resistance and an increase in cytoplasmic calcium ions (Ca^{2+}) during late stages of infection (Y. Kim et al., 2023). This decrease was blocked by benidipine, a wide-range dihydropyridine calcium channel blocker, which prevented these effects, but not by nifedipine, another cardiovascular dihydropyridine channel blocker specific for L-type Ca2+ channels (Y. Kim et al., 2023). Neither drug was bactericidal (Y. Kim et al., 2023). These findings suggest that *R. parkeri* disrupts endothelial cell monolayer integrity through effects on benidipine-sensitive T- or N/Q-type Ca^{2+} channels, and further that benidipine and related drugs should be investigated as potential complementary therapeutics for *Rickettsia*-induced vascular failure.

Conclusion

Over the past few years, there have been advancements in tick-borne disease treatment as well as continued challenges. Recent research has enhanced our understanding of the safety and efficacy of antibiotics such as doxycycline for Lyme disease in young children, providing evidence that it can be a viable alternative to amoxicillin despite concerns about dental staining. Additionally, efforts to identify narrow-spectrum antibiotics for *B. burgdorferi* have shown promise, potentially reducing the risks associated with long-term use of broad-spectrum antibiotics.

The impact of the COVID-19 pandemic on health care has also been highlighted, particularly regarding the delays in diagnosis and treatment of rickettsial infections. The increased reliance on telemedicine and decreased use of emergency departments during the pandemic resulted in longer times to diagnosis and treatment, which could negatively affect patient outcomes. Furthermore, research into pathophysiological mechanisms, such as the disruption of endothelial cell integrity by *R. parkeri*, has identified potential therapeutic targets such as benidipine-sensitive calcium channels. These findings open new avenues for the development of complementary treatments to manage the vascular complications of rickettsial infections.

Overall, the studies reviewed underscore the importance of continued research into both the clinical management and underlying mechanisms of tick-borne diseases, aiming to improve patient outcomes through more effective and targeted therapeutic strategies.

Discussion

The aim of this literature review was to provide an updated analysis of tick-borne disease research published from July 1, 2022, through December 31, 2023. This review outlines the scope of publications and the trends in research concerning tick-borne diseases and associated illnesses during this period. The inclusion and exclusion criteria, detailed in Table 2, were carefully refined throughout the scoping review to encompass a wide range of literature while ensuring the review's thoroughness.

The review findings indicate a steady increase in published works since 2018, with the highest number of articles related to these topics appearing in 2023. To provide additional insights, publications were categorized according to the themes outlined by the 2022 Tick-Borne Disease Working Group, offering an alternative perspective on the literature. Notably, clinical presentation and pathogenesis were identified as dominant themes in the current scoping review, representing 44% of the articles, whereas in the previous review, they comprised only 4% of the scoped literature.

Despite this progress, critical areas such as prevention, public and clinician education, integrated tick management, and climate change remain underexplored in domestic literature. Research efforts directed in these areas face considerable challenges and knowledge gaps, impeding substantial progress in combating tick-borne diseases and associated illnesses comprehensively. While some strides have been made in understanding and interventions, significant limitations persist, highlighting areas where our knowledge remains insufficient.

For instance, efforts focused on preventing tick-borne pathogen transmission have shown promising results with interventions such as acaricidal wall treatments and specialized dog collars, which have led to significant reductions in infection rates for diseases such as RMSF (McCarthy & Wallace, 2023). Similarly, the development of novel antibiotics such as tolfenpyrad targeting B. burgdorferi, the causative agent of Lyme disease, presents new avenues for infection control (A. Clarke et al., 2023). Vaccine development is also pivotal in combating these diseases. Studies have identified reactive antigens and tested vaccine candidates such as VLA15, which targets OspA serotypes, demonstrating promising outcomes (Bézay et al., 2023; Loomba et al., 2023). Additionally, leveraging lipid nanoparticle-encapsulated nucleoside-modified mRNA (mRNA-LNP) platforms have shown potential in developing vaccines against Lyme disease. This approach mirrors the successful model of COVID-19 vaccines and emphasizes a multifaceted strategy encompassing control measures, novel therapeutics, and vaccine innovations (Pine et al., 2023).

On the educational front, studies emphasized the importance of public education and awareness campaigns regarding tick-borne diseases and tick prevention. One study emphasized the need to educate international travelers about the risks of tick-borne diseases and the benefits of vaccination, especially for those engaging in outdoor activities (Poulos et al., 2022). Another study highlighted knowledge gaps among farmers in Illinois, underscoring the necessity of targeted educational efforts to promote effective prevention measures (Chakraborty et al., 2023). In areas such as Long Island, New York, and Maine, studies emphasized the role of public education in shaping risk perceptions and motivating individuals to adopt preventive measures against tick bites and tick-borne diseases, including paying for tick control services and practicing tick bite prevention strategies (Cuadera et al., 2023; Olechnowicz et al., 2023). Additionally, a study in Staten Island, New York, emphasized the need for targeted educational campaigns to inform park visitors about tick hazards and the importance of tick checks and preventive measures while enjoying outdoor activities (Hassett et al., 2022). These findings collectively emphasize the critical role of tailored public education in reducing the risk of tick bites and tick-borne diseases and associated illnesses across different populations and settings.

Moreover, clinician education and awareness are paramount in diagnosing and managing tick-borne illnesses effectively. Limited awareness and knowledge among health care providers have been identified as significant factors contributing to underdiagnosis and inadequate management of AGS (Carpenter et al., 2023; McGill, et al., 2023). Similarly, challenges in diagnosing transfusion-transmitted babesiosis highlight the ongoing need for provider vigilance and education, particularly in non-endemic areas (Costa et al., 2023). Survey data among nurse practitioners underscored gaps in knowledge related to Lyme disease prevention, diagnosis, and treatment, indicating the necessity for ongoing education and resources (Brummitt et al., 2022; Gyura et al., 2023). These findings collectively emphasize the importance of continuous education initiatives to enhance clinician understanding of emerging infectious diseases, improve diagnostic accuracy, and facilitate informed decision-making in patient care.

Interestingly, while the literature on climate change's impact on tick-borne diseases and associated illnesses is sparse within the domestic literature, a notable study discussed the ecological impact of fire suppression on tick populations and disease transmission in the eastern United States (Gallagher et al., 2022). This broader ecological perspective suggests that addressing environmental factors alongside traditional prevention strategies may be key to mitigating the increasing incidence of tick-borne diseases and associated illnesses in human populations. Suggestions such as using prescribed fire to manage tick habitats underscore the need for interdisciplinary approaches in tackling these complex health challenges.

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