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REVIEW ARTICLE

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Tick-borne mix infection diagnosis, challenges, and current practices

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ABSTRACT

Introduction. Tick-borne infections (TBIs) are increasingly recognized as a public health concern in North America and Europe, with Lyme disease being the most notable. The Centers for Disease Control and Prevention (CDC) acknowledges that official statistics likely underestimate the true incidence of TBIs due to diagnostic challenges and underreporting. Co-infections, where multiple pathogens are transmitted through a single tick bite or multiple bites, complicate diagnosis and treatment, leading to more severe symptoms and longer illness durations. Studies indicate a significant percentage of Lyme disease patients also have co-infections, with babesiosis being a common co-infection.

Materials and methods. A comprehensive narrative literature review was conducted using PubMed and Scopus, resulting in 52 manuscripts. Additional reports from the CDC and European Centre for Disease Prevention and Control (ECDC), as well as relevant academic books, were included to meet the study's objectives. The Elicit platform was utilized to enhance reference identification and information synthesis.

Results. The paper provides an overview of tick-borne co-infections, emphasizing the diagnostic challenges posed by overlapping and nonspecific symptoms. It discusses various diseases, including Lyme disease, babesiosis, anaplasmosis, ehrlichiosis, Rocky Mountain spotted fever, and tick-borne encephalitis, detailing their causative organisms, vectors, clinical features, and common co-infections. The review critically examines diagnostic methods such as serological tests, molecular tests, and blood smears, highlighting issues like the „window period" false negatives/positives, and differentiating active from past infections. It also explores emerging technologies and biomarkers, including multiplex assays and next-generation sequencing, which enhance detection capabilities but face challenges in data analysis and standardization.

Conclusions. Accurate diagnosis is crucial to manage these infections effectively, particularly in vulnerable populations. The rise in co-infections and inadequate testing presents a significant public health challenge, necessitating improved surveillance and diagnostic approaches.

Keywords: tick-borne infections, coinfections, TBIs, diagnosis, challenges.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

The prevalence of tick-borne co-infections in humans, both globally and specifically in Moldova, is largely unknown or poorly understood. The true number of tick-borne disease cases may be much higher than reported, due to underreporting and lack of testing, as many patients are not tested, especially if symptoms appear late or if they do not recall a previous tick bite.

The research hypothesis

Patients with tick-borne co-infections are at higher risk of delayed

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or inaccurate diagnoses and more severe clinical outcomes compared to patients with single tick-borne infections, due to overlapping symptoms and limitations of current diagnostic methods.

The novelty added by the manuscript to the already published scientific literature

It consolidates disparate information on diagnostic challenges, current practices, and emerging technologies in the field of tick-borne co-infections into a single structured document; it also explicitly highlights what is not yet known, potentially guiding future research directions.

Introduction

Tick-borne infections are a growing public health issue in North America and Europe, caused by various pathogens (bacteria, viruses, protozoa) transmitted through tick bites [1]. The Centers for Disease Control and Prevention (CDC) reports an increasing trend in these infections, particularly Lyme disease, but admits that official statistics likely underestimate the true incidence due to diagnostic challenges and underreporting [2].

Managing tick-borne infections (TBIs) is complicated by co-infections, where a single tick bite can transmit multiple pathogens or multiple ticks can infect a person [3]. Epidemiological data show that 4% to 45% of Lyme disease patients also have co-infections, which often lead to more severe symptoms and longer illness duration [4]. A recent study found that 42% of babesiosis patients were co-infected with another tick-borne disease, with Lyme disease being the most common co-infection in 41% of those cases [5].

Accurate and timely diagnosis of tick-borne coinfections is essential for effective patient management, reducing morbidity, and preventing severe, potentially life-threatening complications, particularly in vulnerable groups such as older adults or immunocompromised individuals [4]. The presence of multiple pathogens significantly complicates the clinical picture, often resulting in overlapping symptoms that may mask underlying infections. Failure to identify all coinfecting agents may result in inadequate or inappropriate treatment, contributing to persistent symptoms and adverse patient outcomes [6].

The rising prevalence of tick-borne co-infections, along with inadequate testing, poses a significant public health challenge. Many patients with co-infections, which worsen disease severity, remain undiagnosed, leading to an underestimation of the true impact of tick-borne infections in clinical practice and surveillance data. This situation calls for a more comprehensive approach to surveillance and diagnosis that accounts for multiple pathogens, ensuring better allocation of public health resources and improved patient care [7,8].

Prominent bacterial agents include *Borrelia burgdorferi*, the causative agent of Lyme disease, and other *Borrelia* species such as *Borrelia mayonii* and *Borrelia miyamotoi*, which cause Lyme-like illness and relapsing fever, respectively. *Anaplasma phagocytophilum* is responsible for anaplasmosis, while various *Ehrlichia* species cause ehrlichiosis. *Rickettsia rickettsii* is the pathogen responsible for Rocky Mountain Spotted Fever (RMSF), while *Rickettsia conorii* is the causative agent of Boutonneuse fever. Other recognized bacterial infections include Southern Tick-Associated Rash Illness (STARI) and tularemia. Among protozoan pathogens, *Babesia* species, particularly *Babesia microti*, are significant causes of babesiosis [1]. Important viral agents include the Tick-borne encephalitis virus (TBEV), Powassan virus, and Crimean-Congo hemorrhagic fever virus [9].

Environmental factors like temperature and humidity affect tick populations and their spread, while invasive plants create favorable conditions for ticks, hosts and pathogens [2]. Co-infections in ticks vary by region, with specific combinations such as *Borrelia burgdorferi-Babesia microti* and *Borrelia burgdorferi-Anaplasma phagocytophilum* being more common in the U.S. and others like *Babesia-Anaplasma phagocytophilum* and *Rickettsia-Anaplasma phagocytophilum* in Europe [3].

Materials and methods

This review was designed as a structured narrative synthesis of current knowledge about tick-borne co-infections, their clinical significance, and the diagnostic challenges they present. To ensure reproducibility and comprehensive coverage, a systematic approach was applied to the identification, selection, and analysis of the relevant literature. A literature search was conducted in PubMed and Scopus between January and June 2025, using a combination of keywords and MeSH terms such as „tick-borne infections," „co-infection," „mixed infection," „Lyme disease," „babesiosis," „anaplasmosis," „ehrlichiosis," „tick-borne encephalitis," „diagnosis," „multiplex assays," and „next-generation sequencing". Boolean operators were used to refine the queries, and the reference lists of relevant articles and reviews were also reviewed to identify additional sources.

The initial search yielded 52 manuscripts. After removing duplicates, titles and abstracts were screened, and potentially relevant studies were assessed in full text. To complement the database search, official reports from the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC), relevant academic textbooks, and additional records retrieved through the artificial intelligence-based Elicit platform were included. The selection was guided by predefined eligibility criteria: peer-reviewed articles and authoritative reports published in English between 2000 and 2025 that addressed the epidemiology, clinical aspects, or diagnostic approaches of tick-borne co-infections in humans were included, while single case reports without broader implications, studies conducted exclusively in animals, and records without accessible full text were excluded. Screening and selection of studies were performed independently by two reviewers, and discrepancies were resolved through discussion to ensure consistency.

From each eligible publication, data were extracted on the type of infection studied, the geographical setting, the diagnostic methods used, and the main clinical or epidemiological findings. The information was thematically synthesized into categories that reflected the study objectives: epidemiology and burden of co-infections, clinical characteristics and outcomes, current diagnostic practices, and advances in emerging technologies such as multiplex testing and next-generation sequencing. Quantitative results, such as prevalence ranges of co-infections or sensitivity and specificity values of diagnostic methods, were reported descriptively, as provided in the original studies.

Overall, the described methodology combines a systematic literature search, clear inclusion/exclusion criteria, independent dual screening, and descriptive synthesis of quantitative results to produce a reproducible and comprehensive narrative summary of the literature on tick-borne co-infections in humans and their diagnoses.

Results

Tick-borne co-infections present a complex clinical picture due to nonspecific and overlapping symptoms, making diagnosis challenging. Patients often experience common symptoms like fever, fatigue, joint and muscle pain, and headaches, which can resemble other viral illnesses or autoimmune disorders, leading to misdiagnosis or delays in treatment [10]. The erythema migrans rash, indicative of early Lyme disease, is not always present, occurring in only 70–80% of cases. Its absence can complicate the initial diagnosis of tick-borne diseases, especially when co-infections are present [9].

With Lyme-Babesia co-infection, patients often present with a greater number and severity of symptoms than those with Lyme disease alone. These may include increased fatigue, headaches, profuse sweating, chills, loss of appetite, emotional lability, nausea, conjunctivitis, and splenomegaly [11].

Co-infection with *Babesia* is also associated with a significantly longer duration of illness in patients with Lyme disease. One study observed that 50% of co-infected patients remained symptomatic for three months or more, compared with only 4% of patients with Lyme disease alone [11]. Rash is not a common symptom of babesiosis, and its presence may suggest co-infection with Lyme disease [12].

Symptoms of anaplasmosis typically include headache, fever, chills, malaise, and muscle aches, with some infections being asymptomatic [13]. The presence of multiple pathogens can lead to overlapping or intensified symptoms, greatly confusing physicians and significantly delaying appropriate treatment [14]. The clinical spectrum of babesiosis alone can range from asymptomatic to severe multiple organ failure, with severity often dependent on the immunocompetence of the host [12].

Polish studies documented lower co-infection rates, with *Borrelia* species co-infections with *A. phagocytophilum* and *Babesia* spp. each occurring at 4.2%. However, in patients with tick-borne encephalitis (TBE), 27% were co-infected with *Borrelia* species, 10.9% with *A. phagocytophilum*, and 0.9% with *Babesia* spp., with triple co-infections (TBE-*Borrelia*-*Anaplasma*) occurring in 2.7% of patients [15].

These co-infections can complicate diagnosis and treatment, as they may exacerbate symptoms or mimic other tick-borne diseases [16]. Co-infections between *Borrelia burgdorferi* s.l. and TBEV are particularly notable, especially in patients presenting with high fever, erythema migrans, or neurological symptoms [17].

An overview of common tick-borne pathogens, detailing the diseases they cause and their main tick vectors, is provided in Table 1. It also highlights the typical clinical features associated with each infection and mentions their common co-infection partners, illustrating the diverse and interconnected nature of tick-borne diseases.

Table 1. Common tick-borne pathogens, associated diseases, and primary vectors

Disease name	Causative organism	Primary tick vector(s)	Key clinical features	Common co-infection organism
Lyme Disease	*Borrelia burgdorferi, B. mayonii, B. miyamotoi*	*Ixodes scapularis, I. pacificus, I. ricinus, I. persulcatus*	Erythema migrans rash (70-80%), fever, chills, fatigue, headache, joint pain, neurological issues	*Babesia microti, Anaplasma phagocytophilum*
Babesiosis	*Babesia microti, B. duncani, B. venatorum, B. divergens*	*Ixodes scapularis, I. pacificus, I. ricinus*	Fever, chills, sweats, malaise, fatigue, headache, splenomegaly, anemia, thrombocytopenia (rash uncommon, suggests co-infection)	*Borrelia burgdorferi, Anaplasma phagocytophilum*
Anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis, I. pacificus*	Fever, chills, malaise, headache, myalgia, cytopenia, liver enzyme abnormalities (rash uncommon, may occur with Borrelia co-infection)	*Borrelia burgdorferi, Babesia* spp.
Ehrlichiosis	*Ehrlichia chaffeensis, E. ewingii*	*Amblyomma americanum, Dermacentor variabilis*	Fever, headache, myalgia, fatigue, cytopenia, liver enzyme abnormalities (rash less common)	*Borrelia burgdorferi, Anaplasma phagocytophilum*

Rocky Mountain Spotted Fever (RMSF)	*Rickettsia rickettsii*	*Dermacentor variabilis, Rhipicephalus sanguineus*	Fever, headache, rash (maculopapular or petechial, often on extremities), myalgia, nausea, vomiting	Other *Rickettsia* spp. (cross-reactivity in tests)
Tick-borne Encephalitis	Tick-borne Encephalitis Virus (TBEV)	*Ixodes ricinus, I. persulcatus, I. ovatus*	Neurological phase: higher fever, severe headache, stiff neck (meningeal signs), confusion or altered mental status, sensitivity to light, dizziness, lack of coordination, tremors, seizures, weakness or paralysis (especially of the limbs or facial nerves)	*Borrelia burgdorferi, Anaplasma phagocytophilum, Babesia* spp.
Powassan Encephalitis	Powassan virus	*Ixodes scapularis, I. cookei*	Fever, headache, vomiting, weakness, confusion, seizures, memory loss, encephalitis	None specified

Limitations of current standard diagnostic methods. Recent studies have highlighted the challenges in diagnosing tick-borne mixed infections. Early diagnosis can be difficult without laboratory confirmation [18]. However, researchers have developed predictive models using clinical and laboratory parameters to differentiate between mixed infections and mono-infections with excellent accuracy [19]. These models incorporate factors such as fever, intoxication syndrome score, and various blood count parameters. To address the limitations of current diagnostic methods, a multiplex, array-based assay called TBD-Serochip has been developed, capable of discriminating antibody responses to eight major tick-borne pathogens [20]. This platform allows for accurate identification of specific immunodominant epitopes, enhancing diagnostic accuracy. Despite these advancements, challenges remain in the molecular and serologic diagnosis of tick-borne co-infections, primarily due to limitations in sensitivity, specificity, and the capacity to include multiple agents in a single assay [6].

Serological tests (ELISA, Western Blot, indirect immunofluorescence assay - IFA). Serological tests primarily detect the host antibody response, which typically takes several weeks to develop. This „window period" often results in false-negative results during the crucial early stages of infection, when treatment is most effective [21]. In contrast, antibodies can persist for years after infection, making it difficult to differentiate between an acute, active infection and a previous exposure. Confirmation of a recent infection usually requires demonstration of a fourfold increase in antibody titers between acute and convalescent samples [22].

Intrathecal antibody production is the gold standard for diagnosing Lyme neuroborreliosis in Europe, particularly with *B. garinii* linked to neurological cases. However, interpreting results is challenging due to the absence of a definitive gold standard, varying case definitions, different assays, and limited comparisons among labs. The sensitivity of detecting intrathecal antibody production in acute cases is approximately 50% [23]. Cross-reactivity with antibodies from other infections is a significant problem, particularly in rickettsial diseases, where serological tests may fail to differentiate between the highly lethal RMSF and similar less severe infections [24]. Many laboratory-developed tests for TBIs are not approved by regulatory bodies, and diagnostic methods are not standardized across clinical laboratories, leading to inconsistencies [25].

Molecular tests (polymerase chain reaction - PCR). Although PCR offers greater specificity and directly indicates active infection by detecting pathogen DNA/RNA, its sensitivity may be limited in early or late infection due to low pathogen burden or transient presence in the bloodstream [6]. In some infections, PCR results may remain positive for months or even years after treatment, complicating the assessment of active infection versus residual genetic material [26].

PCR for detecting *Rickettsia* is a powerful tool but has limitations, such as the risk of false negatives in early infections or low bacterial loads. Sensitivity can vary based on the timing of sample collection and the specific *Rickettsia* species, and PCR assays may struggle to differentiate between closely related species [27,28].

PCR methods present significant advancements in diagnosing Lyme disease, particularly through digital PCR, which enhances sensitivity by detecting *Borrelia burgdorferi* DNA even at low levels. This technique effectively addresses challenges related to low spirochete counts by utilizing larger sample volumes and pre-examination processing, with platelet-rich plasma being particularly useful [29]. However, standardization is essential due to variability in results among laboratories. While PCR is highly specific and sensitive, its effectiveness is influenced by several factors, highlighting the need for standardized protocols to ensure consistent results [30].

Molecular methods are effective for detecting tick-borne encephalitis virus RNA in ticks and clinical samples. Nested RT-PCR targeting the NS5 gene and real-time PCR targeting the E gene have been developed for epidemiological surveillance and strain identification [31,32]. However, the diagnostic utility of PCR in clinical samples is limited, as positive results are typically only obtained early in the disease, making serological diagnosis more reliable for patient care [33].

Blood smear examination (for babesiosis, anaplasmosis). Direct microscopic examination of peripheral blood smears can diagnose babesiosis and anaplasmosis, but it is a laborious method that requires a highly skilled specialist. In early infection, the parasite load may be low, requiring examination of multiple smears to increase the sensitivity of detection. Morphological similarities can lead to misinterpretations, such as confusing ring forms of *Babesia* with *Plasmodium falciparum* [12].

Overview of standard methods for individual infections. The standard diagnostic approach for Lyme disease involves a two-tiered serological testing method, typically starting with an ELISA followed by a confirmatory Western blot. Modified tests like multi-antigen ELISA or C6 ELISA are also used [34]. However, serological tests can be misleading, as they may be negative early in the infection and can remain positive for years, complicating the distinction between active and past infections [35].

Babesiosis diagnosis is primarily made by identifying the *Babesia* organism in a Giemsa- or Wright-stained blood smear, looking for ring shapes and tetrads (Maltese crosses). Due to potentially low parasite loads in early infection, multiple smears are recommended for better detection. PCR testing provides higher sensitivity than smears, while serology, especially indirect immunofluorescent antibody testing, can confirm the diagnosis but requires a fourfold increase in titers to indicate a recent infection [9].

Anaplasmosis diagnosis involves various methods such as culture, histopathology, PCR, and serology. A key diagnostic indicator is the presence of morulae, which are characteristic intracytoplasmic aggregates found in neutrophils, detectable in 20–80% of symptomatic patients, particularly during the first week of infection. Confirmation of the diagnosis often relies on serological tests or blood smear examination [36].

For ehrlichiosis, similar to anaplasmosis, the diagnosis is frequently confirmed by serologies or blood smears. While serology can confirm past infection, PCR is generally more useful for detecting active infection. Although PCR tests are available for *Ehrlichia*, their widespread accessibility and speed for real-time clinical decisions remain limitations [37].

Diagnosis of tick-borne encephalitis virus (TBEV) primarily relies on serological methods, as viral RNA is seldom detectable during neurological symptoms. TBEV-specific IgM ELISA tests in serum and cerebrospinal fluid (CSF) demonstrate high sensitivity and specificity (94-100%) for diagnosing tick-borne encephalitis in humans. However, IgG ELISAs may lack specificity due to potential cross-reactions with other flaviviruses and require confirmatory virus neutralization. The presence of intrathecal TBEV IgG synthesis can support the diagnosis in chronic cases, with about 55% of TBE cases showing this response. In immunocompromised patients, detecting TBEV RNA in CSF might be necessary for accurate diagnosis [38–40].

The diagnosis of Rocky Mountain spotted fever, like other tick-borne rickettsial diseases, is usually based on a combination of clinical symptoms and epidemiologic evidence. Serological tests, particularly the indirect immunofluorescence test, are considered the gold standard for rickettsial infections. PCR testing can confirm an active infection, but a negative PCR result does not definitively rule out RMSF [41].

Emerging diagnostic technologies and new biomarkers. Recent advancements in multiplex testing platforms have improved the diagnosis of tick-borne infections. New array-based assays can differentiate antibody responses to eight major pathogens, while real-time multiplex PCR assays enable quick and cost-effective screening for *Borrelia burgdorferi, Anaplasma phagocytophilum*, and *Babesia microti*. Additionally, a customizable multiplex protein microarray enhances sensitivity and specificity by detecting multiple antibodies simultaneously. A multiplex qPCR method has also been developed to efficiently detect *Ehrlichia* spp., *Rickettsia* spp., and *Borrelia* spp. in one reaction. These innovations significantly enhance the molecular diagnosis of tick-borne diseases, facilitating earlier intervention and better patient outcomes [20,42–44].

Beyond direct pathogen detection, research is actively exploring novel host-response biomarkers that could improve the diagnosis and monitoring of tick-borne infections and co-infections. Standard clinical markers, such as cytopenias and liver function test abnormalities, are already recognized as typical laboratory findings in tick-borne diseases and can aid in diagnosis [37]. Studies have investigated various immune biomarkers, including CD57+ and CD19+ lymphocyte counts, CD3%, CD4%, CD4+ Helper T cell count, CD4+/CD8+ ratio, white cell count, and total IgG. Notably, a significant percentage of patients with clinically diagnosed tick-borne infections exhibited low CD57+ counts. Changes in iron studies, specifically transferrin and transferrin saturation percentages, have also shown statistically significant alterations in TBI patients before and after antibiotic treatment, suggesting their potential as diagnostic or prognostic markers [45,46]. For tick-borne encephalitis, specific immunoglobulins, free light chains, metalloproteinases, and cytokines show promise as biomarkers [47].

The latest evolution in sequencing technologies, particularly next-generation sequencing (NGS), has greatly enhanced the detection and characterization of tick-borne pathogens. Techniques such as the TBDCapSeq assay, which utilizes hybridization capture probes, have shown superior sensitivity compared to traditional PCR methods, allowing for the identification of a broader range of pathogens, including previously unknown infections and co-infections [48,49]. Additionally, a 16S rRNA gene PCR followed by NGS has demonstrated effectiveness in detecting tick-borne bacteria in whole blood [50]. Nanopore adaptive sampling (NAS) further improves biosurveillance by enabling real-time enrichment of targeted sequences, facilitating the simultaneous detection of multiple pathogens. These advancements underscore the complexity of microbial communities associated with ticks and emphasize the need to study the entire pathobiome. Despite these promising developments, challenges in data analysis, particularly in understanding complex microbial interactions, remain a significant hurdle [51,52].

A summary comparison is provided in Table 2 on various diagnostic methods used for tick-borne co-infections, including traditional approaches such as blood smears and serology, alongside emerging technologies such as multiplex assays and sequencing. It outlines the strengths, limitations, and optimal use cases for each method, highlighting the continuing advances in the detection of these complex infections [25].

Table 2. Comparison of diagnostic methods for tick-borne coinfections

Diagnostic Method	Primary Pathogens Detected	Key Strengths	Key Limitations	Optimal Use Case
Blood Smear	*Babesia*, *Anaplasma*	Direct visualization of parasites, can assess parasitemia	Requires skilled microscopist, time-consuming, low sensitivity in early infection (low parasite burden), misinterpretation risk (e.g., *Plasmodium*)	Acute babesiosis/ anaplasmosis, initial suspicion
Serology (ELISA/ Western Blot/IFA)	*Borrelia*, *Babesia*, *Anaplasma*, *Ehrlichia*, *Rickettsia*, TBEV	Relatively accessible, can confirm exposure	Low sensitivity in early infection (window period), cannot distinguish active vs. past infection (single positive), variable antibody responses, cross-reactivity, low completion rates for two-step tests	Later stage infection, confirmation of exposure, epidemiological studies
PCR (Molecular Assays)	*Borrelia*, *Babesia*, *Anaplasma*, *Ehrlichia*, *Rickettsia*, *B. miyamotoi*	Direct detection of pathogen DNA/RNA (active infection), high specificity, can detect multiple strains	Sensitivity limited by transient/ low pathogen burden, can remain positive post-treatment, not widely accessible/fast enough for all pathogens (e.g., *Rickettsia*), expensive	Early acute infection, immunocompromised patients, confirmation of active infection
Multiplex Assays (e.g., Protein Microarrays, Chemiluminescent Arrays)	Multiple pathogens (e.g., *Borrelia*, *Babesia*, *Bartonella*, *Anaplasma*, *Ehrlichia*)	Broad-spectrum detection in single run, enhanced diagnostic efficiency, reduced turnaround time, improved sensitivity/specificity for multiple agents, reduced cross-reactivity (specific peptides)	Regulatory hurdles, complex validation for multiple analytes and interactions, may still rely on antibody detection (window period)	Comprehensive screening for co-infections, differential diagnosis of overlapping symptoms
Next-Generation Sequencing (NGS)	Broad range of known and potentially novel pathogens	High-throughput, can detect novel/ unsequenced pathogens, large number of probes, reduces lab equipment needs	High cost, complex data analysis, not yet standard for routine clinical use, still may face challenges with very low pathogen loads	Research, complex/ unresolved cases, pathogen discovery
Novel Biomarker Panels (e.g., Immune markers, Metabolomics, Peptidoglycan fragments)	Host response to infection, PTLDS	Potential for earlier detection, differentiation of active vs. past infection, objective measures for post-treatment syndromes, insight into host-pathogen interaction	Still largely research-based, lack of clinical validation and standardization, complex interpretation, not yet widely available clinically	Research, future diagnostics for early disease and PTLDS, monitoring treatment response

Note: *ELISA - Enzyme-linked immunosorbent assay; IFA - Indirect immunofluorescence assay; PCR - polymerase chain reaction; TBEV - Tick-borne encephalitis virus; PTLDS - Post-Treatment Lyme Disease Syndrome.*

Discussion

The complexities of co-infections in tick-borne diseases highlight significant limitations in current diagnostic tools, which often fail to detect a wide range of pathogens due to the variable presence of microbial DNA/RNA or antigens. This results in missed diagnoses and inadequate treatments, as patients are rarely tested for all potential tick-borne agents. Additionally, the differing transmission rates of pathogens complicate diagnostic approaches. These deficiencies lead to increased healthcare costs and prolonged patient suffering, while also hindering public health efforts and research. There is an urgent need for a shift toward integrated, multi-pathogen testing strategies to improve patient outcomes and control the spread of these diseases [53].

The increasing prevalence and complexity of tick-borne co-infections impose a substantial economic and public health burden. Lyme disease alone is estimated to cost the U.S. healthcare system between $712 million and $1.3 billion annually in direct medical costs, averaging nearly $3,000 per patient in follow-up visits and testing. Patients with Lyme disease and Post-Treatment Lyme Disease Syndrome (PTLDS) incur significantly higher healthcare costs, with one study finding an additional $3,798 in costs compared to those without post-treatment symptoms [54,55]. The challenges in diagnosis and treatment, particularly for co-infections, amplify patient suffering and contribute to these rising healthcare costs.

Tick-borne encephalitis (TBE) presents a significant and increasing burden in many European countries, including Slovenia and Sweden. Studies have used disability-adjusted life years (DALYs) to quantify the burden, with Slovenia reporting 3,450 DALYs (167.8 per 100,000 population) in 2011. Permanent sequalae contribute most to the total burden, emphasizing the importance of vaccination as a preventive strategy [56,57]. In Sweden, a 17-year study revealed that TBE patients had significantly more hospitalizations, specialist outpatient visits, and sick leave days compared to the general population, with differences increasing over time [58]. The true burden of TBE may be underestimated, as shown in Italy's Veneto region, where only 80.8% of cases were reported through mandatory notifications [59].

The Altai region of Russia faces a heightened risk of tick-borne diseases, with spotted fever group rickettsiosis being the most significant, contrary to the national prevalence of Lyme borreliosis. The growing threat is compounded by suboptimal diagnostics, limited treatment options for emerging pathogens, and a lack of vaccines. Mixed infections and poorly studied pathogens further complicate the landscape of tick-borne diseases, highlighting the need for improved prevention and management strategies [54,60].

Conclusions

Addressing the challenge of tick-borne co-infections requires a comprehensive strategy that includes increased investment in research into advanced diagnostic tools and biomarkers. Optimizing regulatory processes is essential to accelerate the clinical availability of these innovations. Raising public and professional awareness of the complex epidemiology and clinical manifestations of these diseases is also crucial. Promoting a more proactive diagnostic approach enables the early detection of tick-borne pathogens, improving treatment strategies and reducing long-term suffering. This multifaceted effort aims to mitigate the significant public health and economic impact associated with tick-borne co-infections.

Competing interests

None declared.

Contribution of authors

OS designed the study, collected, and analyzed the data. GB critically revised the manuscript and analyzed the data. Both authors reviewed the work critically and approved the final version of the manuscript.

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