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Review Article **Open Access**

Lyme disease: ecological and epidemiological factors influencing increased global transmission

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Abstract

Lyme disease (LD) has experienced a significant surge in prevalence over the last 20 years, spreading rapidly across the globe. This worrisome trend can be attributed to several factors, including the proximity of humans to LD carriers, heightened clinical awareness of the disease, and the expansion of tick habitats due to climate change. The encroachment of urban development has brought communities closer to ticks that carry LD, yet our understanding of LD lags behind, particularly in terms of the genetic makeup of various LD strains. Although attempts have been made to bridge this knowledge gap through citizen science initiatives and improved accessibility to testing, the scarcity of data in resource-poor regions remains a formidable obstacle to overcome. There is a significant gap in the identification and management of LD in regions where there is no clinical awareness of the disease and limited resources for research dissemination. It is essential to collect comprehensive data to identify LD effectively so that healthcare workers can promptly diagnose infected patients. Urgent action is necessary to prevent future health crises and reduce costs, as the spread of LD is increasing year after year. Climate change is partly responsible for this surge in cases, and researchers must adapt flexible data collection methods to control its spread. Improved community-level monitoring for LD, clinical recognition, and broader research dissemination can improve patient care, inform public health strategies, and secure funding for further research.

Keywords: Epidemiological data, Lyme Disease, Lyme recognition, Prevalence, Ticks.

Introduction

Lyme disease (LD), commonly known as *Lyme borreliosis*, is a common disease spread by ticks in numerous parts of the world.[1] It is caused by a bacteria called Borrelia burgdorferi and develops in stages. The early stage of LD is typically characterized by a bullseye rash that appears at the tick bite's location, usually on the armpits, neck, and legs.[2] This stage may last for 1-2 weeks, after which the disease progresses to the next stage, which may include flu-like symptoms, joint pain, and neurological issues.[3] During the late disseminated or chronic stage of LD, patients may experience neurological issues such as numbness and drooping of one side of the face, as well as joint problems like swelling and reduced motion. It is crucial to identify and treat LD with antibiotics in the early stages to prevent more severe problems from occurring. While doxycycline, an oral drug, can be used in patients with early-stage LD,[4] those with later-stage disease are treated with ceftriaxone, a drug that can be administered directly into the bloodstream and is just as effective as doxycycline.

LD is primarily spread through tick bites, with deer ticks being the most common carriers of the disease.[5] Cases of LD are most frequently found in grassy and wooded areas. The disease was first discovered in Lyme, Connecticut, which is a state in the northeastern US with a temperate climate and wooded ecosystems. It was in the 1980s that a decades-long medical mystery was solved, and the Borrelia burgdorferi bacterium was identified as the cause of the mysterious illness.[6] LD is a widespread illness that affects people in several parts of the world, such as the Northeastern US, Central and Northern Europe, West

Asia, and other regions.[7] However, LD is gradually spreading to new areas, even urban areas, due to various factors such as human activities, increased monitoring, climate change, deer habitat change, and alterations in native ecosystems, among others.[8,9] With the rising number of patients infected with LD, it is important to properly train healthcare providers who may not have had prior experience dealing with the disease. This training should focus on the prevention, recognition, and treatment of LD in regions with outbreaks. By improving these measures, we can reduce the human and financial toll of LD and provide better care to those affected. In this paper, we will examine the reasons behind the increasing prevalence of LD, as agreed upon by the literature, by looking at specific cases. We will then discuss the underlying cause for all of these reasons, how they contributed to our findings, and what the scientific community can do to mitigate them.

1. **Human activities**

Human activity greatly contributes to the spread of LD to new areas, according to research. Various pathways have been identified as sources of human-induced LD expansion.[10]

2.1 Habitat encroachment

TDisruptions in the natural habitat of ticks carrying LD contribute to its spread. One such disturbance is habitat encroachment, which happens when human development takes over land and disrupts the native ecosystems, resulting in humans being in closer proximity to those ecosystems.[11] Urban development is a significant driver of such encroachment, where urban and suburban areas are built on land that was previously forested and tick-infested, putting humans in close proximity to ticks.[12] For example, from 2004 to 2011, the incidence rate of LD in Baltimore, Maryland, increased by 13% annually.[13] This increase can be linked to human development, as seen in the case of the Baltimore Zoo, which was constructed on Druid Hill Park, a large wooded park located within the city's boundaries.[14]

An investigation was launched after an employee at the Baltimore Zoo presented with a bulls-eye rash and other standard early-stage LD symptoms. As the employee had not traveled outside the city recently, it was believed that they contracted the disease in Druid Hill Park, where the zoo is located. Although no other zoo employees tested positive for LD, researchers decided to trap animals and test ticks and bacteria that cause LD. Over the course of three months, they found nine ticks and two mice with the bacteria. Although the risk of humans getting infected with LD is still considered low, it may increase as more people visit parks and live closer to ticks due to urbanization. This is especially concerning in periurban areas where humans are in close proximity to ticks, as it could lead to an increase in cases of LD in the future.

2.2 COVID-19 and quarantine

In recent years, there has been a documented increase in LD. This rise could be attributed to changes not only in animal habitats but also in our own living conditions and habits. As we change our lifestyles, the severity and spread of LD also change accordingly.[15] One of the most severe changes of the twenty-first century was the COVID-19 pandemic produced by the SARS-CoV-2 virus.

Due to the widespread lockdown and heightened skepticism towards common cold symptoms, or even LD symptoms in some instances, being mistaken for COVID-19 and resulting in a mandatory 14-day isolation, LD had the potential to escalate without proper attention. This could ultimately result in deteriorating patient conditions as LD progresses over time without adequate care.[16] An example of such a case was identified in New York.

Upon arrival at the hospital, this patient exhibited a decreased heart rate, dizziness, and respiratory difficulties, accompanied by the characteristic "bulls-eye" rash. These symptoms indicated severe complications.[17] Despite the presence of the rash, which raised suspicion of LD, and the administration of IV Ceftriaxone, the patient experienced a cardiac arrest while at the hospital. The patient made a full recovery and was released within a span of four days. Simultaneously, as the hospital concluded its operations, scientists uncovered that the patient had arrived at the emergency room after completing a 14-day COVID-19 quarantine, having traveled to upstate New York beforehand. There is a suspicion that the patient was bitten and contracted LD near the beginning of the quarantine period, as the onset of severe symptoms coincided with the

14-day mark, which aligns with the usual timeframe for severe LD symptoms to manifest. If the quarantine had been extended, the patient could have experienced a cardiac arrest within the boundaries of their own home without any assistance. At the very least, they would have endured a longer period of suffering. This instance serves as a clear demonstration of how seemingly unrelated factors in our society, such as the recommended 14-day quarantine period, can have significant impacts on our health and the advancement of LD.

2.3 Human-mediated thoroughfare

In contrast to the slower dissemination but more severe instances observed during quarantine, the rapid urbanization of the world has resulted in an acceleration of human systems such as transportation, community development, and habitat encroachment. Recent trends indicate that LD is spreading over larger distances and at a faster rate compared to the past. A notable example of this is the spread of LD in urbanizing regions of the Northeastern US. LD has historically been a prevalent issue in the Northeast US, as previously discussed. However, the growth of cities and enhanced connectivity between them, particularly in periurban areas, has exacerbated this problem. These areas, located on the outskirts of cities, are witnessing an increase in both ticks and the human population.[18] The enhanced flow of vehicles and the higher frequency of vehicles resulting from improved transportation systems connecting cities in the Northeast have resulted in a wider spread and a more abundant occurrence of LD. A prime illustration of this is the I-95 mega highway, stretching from Maryland to Maine, where a significant portion of this urban expansion is occurring.[19] Researchers have postulated that the I-95 highway could potentially facilitate the transmission of LD. This is due to the possibility that ticks, which carry the disease, may be able to travel along the highway and migrate into cities and neighboring regions. The expansion of suburban development into previously rural areas, where ticks are more commonly found, has further exacerbated this issue. These expansive highways, such as I-95, allow for the rapid transportation of ticks from rural to urban environments. The study focused on an extensive area spanning 50 miles (80.47 km) on each side of I-95, encompassing a total of 25.0 million acres. Over the course of a decade, cases of LD were documented within this region. The investigators monitored the incidence of LD occurrences throughout a specific period and established a robust correlation between urban expansion and the frequency of LD cases. Regions undergoing a transition from rural to suburban to urban landscapes exhibited a higher prevalence of the disease in comparison to areas with minimal urban development. Cities served as focal points for the disease, with surrounding regions generally experiencing a greater number of cases. Furthermore, a discernible association was observed between the proximity to I-95 and the occurrence of LD cases. The correlation between urbanization and cases of LD is not solely attributed to the intrusion of humans into the habitats of tick-carrying animals.[20] The expanded range of ticks' movement enables the emergence of cases not only in rural regions but also in urban areas, indicating a growing impact of urbanization on the spread of the disease.[21]

3. Increased monitoring

The epidemiology and geographic distribution of LD are undergoing changes, indicating the dynamic nature of the disease. However, the identification of LD is a relatively recent development. Consequently, in regions where LD is not prevalent, serologic testing is necessary to confirm the diagnosis.[22] Unfortunately, the accessibility and reliability of such testing are often limited in underdeveloped healthcare settings. Hence, the actual occurrence of LD is frequently concealed. Nonetheless, as LD-specific monitoring has expanded in many geographical regions, particularly in rural areas, the apparent rise in LD cases may be ascribed to the existing prevalence, which can now be discovered by diagnostic procedures.[23] As LD continues to spread into previously unaffected regions, it is crucial for physicians to actively monitor, identify, and consider LD in their diagnostic process. This approach will facilitate precise reporting and enhance patient outcomes.

3.1 Testing in rural areas

It is crucial to have dependable testing methods for LD in rural regions in order to accurately determine the presence of LD.[24] Two commonly employed tests are ELISA and a confirmatory Western Blot test.[25] ELISA, also known as an enzyme-linked immunosorbent assay, is capable of identifying the quantity of a particular enzyme in a bodily sample. However, it exhibits a low accuracy rate of approximately 80% at best and is prone to producing a significant number of false negatives.[26] In contrast, Western Blot exhibits a remarkable level of precision (99.9%), albeit at a significantly higher expense.[27,28] Although Western Blot and culturing are the prevailing methods of testing, an alternative approach involves directly cultivating the bacteria, allowing for visual identification.[29] Nevertheless, culturing poses challenges due to the Borrelia bacteria's relatively sluggish growth rate and its specific requirements for optimal growth conditions such as oxygen, pH, and temperature.[30] In addition to the aforementioned obstacles faced by all Borrelia bacteria, there exists a significant amount of genetic variation among the Borrelia bacteria responsible for causing LD worldwide.[31] This genetic diversity has resulted in the absence of a universally standardized culture method, as the bacteriophages from different regions necessitate distinct culturing mediums and procedures.[32–34]

In 1994, a comprehensive investigation was conducted on two individuals residing in Menominee County, Michigan, United States. This county is predominantly rural and was not previously recognized for having cases of LD.[35] The healthcare facilities in this rural region were not well-versed in the identification and typical symptoms of LD. Consequently, diagnostic tests for LD were not administered during that period. The study observed two patients who exhibited the characteristic erythema migrans, commonly referred to as the "bulls-eye" rash, which is a prominent indicator of LD. What set these cases apart was the doctors' decision to conduct a skin biopsy on the distinctive "bulls-eye" mark and subsequently perform a bacterial culture to validate the presumed existence of LD in these individuals. This occurrence marked the initial instance in which such an examination was documented in a rural healthcare facility in Michigan for the detection of LD, as the process of culturing is usually challenging. Both individuals promptly received medical intervention and experienced rapid clinical improvement without any complications. Presently, there has been a noticeable increase in the number of confirmed cases of LD in Menominee County, which can be attributed, at least in part, to the growing awareness among healthcare professionals and the utilization of diagnostic methods to validate the presence of LD.

3.2 Recognizing Lyme disease (LD)

Nevertheless, the efficacy of conducting suitable LD testing alone is rendered futile in the absence of prior clinical suspicion. In regions where LD has not been historically prevalent, a lack of clinical suspicion is a common occurrence.[36,37] Symptoms of LD, apart from the distinctive bulls-eye rash, are generally nonspecific and can be similar to those of various other ailments. Consequently, the presence of clinical suspicion for LD is crucial, but it may often be lacking if there is no previous record of the disease in the particular area. This phenomenon has been observed in Brazil, where the prevalence of LD has been on the rise since the first documented case in 1992.[38]

In the year 2012, an investigation was carried out in the rural region of Tocantins, Brazil, where three individuals were officially diagnosed with LD.[22] This occurrence represented the initial confirmed instances of the disease in that particular state. Tocantins encompass both the Amazon rainforest and savanna, harboring a diverse range of animal species that serve as hosts for ticks, known carriers of LD.[39,40]

Ticks are usually found in areas populated by people. Nevertheless, the diagnosis of LD in Brazil poses a challenge due to the need for a comprehensive assessment involving clinical symptoms, a record of tick bites, and a serologic antibody test for confirmation. This task becomes arduous as the characteristic "bulls-eye" rash, which is typically associated with LD, is not frequently observed in patients with the disease. In fact, a study indicates that this rash is present in only approximately 6 out of 19 patients.[41] Hence, it is crucial to consider the pre-existing clinical suspicion when considering LD as a potential cause of illness in these patients. Consequently, the identification and treatment of LD in its early stages, before it progresses into a chronic condition, pose significant challenges.[36,42,43] Furthermore, the problem is exacerbated by the fact that Borrelia burgdorferi, the bacterium responsible for LD, has yet to be properly cultivated in humans or animals, and research in laboratory settings has been restricted. This lack of isolation and limited research hamper efforts to enhance the precision of serological antibody testing for LD.[22]

In the analysis of the three patients from Tocantins, a comparable pattern surfaced. The first patient, a youthful rural laborer, endured fever and joint discomfort for a duration of one month. Despite consulting with multiple medical professionals, it wasn't until he sought the advice of an infectious disease specialist and mentioned getting bitten by ticks that the suspicion of LD was raised. A pruritic and inflamed rash appeared on his legs at the location of the tick bite, prompting serologic testing to confirm the diagnosis. Consequently, he received treatment with tetracycline, an antibiotic. In a separate incident, a female individual paid a visit to a countryside farm and encountered a tick bite. Following several weeks, she was admitted to the medical facility due to symptoms resembling dengue fever, such as fatigue, bodily discomfort, elevated body temperature, and a tingling sensation in her hands known as paresthesia. Initially, she was discharged with the belief that rest would suffice for her recovery. However, she reappeared at the hospital the following day with significantly aggravated symptoms, including pain in the abdomen and chest, heartburn, and an unhealthy complexion. Despite conducting extensive biochemical and electrolyte examinations, no noteworthy abnormalities were detected. Nevertheless, her pain and illness progressively worsened over the course of several days. Physicians started suspecting LD as the patient continued to experience joint pain even after her other pain had reduced, eight days after her initial presentation. Following LD-specific treatment, she made a complete recovery. The lack of LD-specific symptoms, compounded by a lack of clinical suspicion in the presence of a tick bite, may have contributed to the delay in appropriately identifying the disorder.

In the third instance, a comparable narrative transpired. A youthful gentleman exhibited non-specific symptoms and experienced a decline in health over a span of eight days. Despite the efforts of physicians, the identification of LD eluded them throughout this duration, ultimately resulting in the demise of the patient. It was only after the patient's passing that the confirmation of LD diagnosis was achieved through Western blot analysis.

In spite of these being the initial confirmed LD cases in Tocantins, speculations regarding LD had already circulated in the area. This research serves as a relevant illustration of how raising awareness and consequently monitoring LD can enhance the number of precise LD diagnoses. However, it takes considerable time for awareness and clinical suspicion to spread and become established in a particular region. While the Michigan Clinic first adopted culturing as part of their diagnostic procedures in 1994, Tocantins physicians only incorporated culturing into their diagnostic practices in 2012. The necessity for awareness, accurate testing, and diagnosis is progressively growing as LD expands its geographical reach. The experiences of individuals from Michigan, Tocantins, and other locations emphasize the urgency for an expanded geographic approach in the diagnosis and treatment of LD.

4. Effects of climate-driven spread

Climate change is driving the geographical growth of LD and its hosts. The traditional environmental factors that support the growth of LD, such as warmer and more humid summer months with shorter winters, are spreading to new areas.[20] However, there are also regions where ticks are becoming less able to survive due to increased drought and reduced snow coverage, which provides insulation for ticks during the winter. Research studies have indicated a rise in LD prevalence in various parts of the world, including the United States, Canada, the Nordic regions, the Arctic, and South America. This expansion of LD due to climate change has significant implications for researchers and healthcare systems.[44]

4.1 Expansion hampers research

As the geographical distribution of ticks widens, it is imperative for public health authorities to monitor the dissemination of LD. This is achieved through the collection of ticks from their native habitats and subjecting them to testing for the presence of the Borrelia bacterium.[45] Nonetheless, implementing this process is not always straightforward. For example, in Canada, a country badly hit by the increasing incidence of LD, officials have struggled to keep up with the disease's fast spread.[46] Efforts have been undertaken to augment the quantity of collection sites. Nevertheless, owing to limited resources, this ultimately resulted in a decrease in the frequency at which researchers could monitor these sites. To address this issue, a potential solution was examined in a study conducted in 2018, which investigated the feasibility of utilizing citizen science to gather essential data.[47] By engaging citizens to venture into the field and conduct their own tests, subsequently sharing the collected data with researchers, the citizen science program proved to be immensely successful, yielding a substantial amount of high-quality data. Undoubtedly, the accomplishments of the Canadian team in this regard represent a noteworthy advancement. The necessity to adjust the team's data collection approach underscores the detrimental impact of climate change. As climate change persists in the future, there will be a greater demand for inventive and adaptable methods of data collection. It is crucial to prioritize surveillance for LD, considering the overall transformation of ecosystems, including not only ticks but also deer, bats, and other carriers. This prioritization is essential to guaranteeing the accuracy and comprehensiveness of the collected data.[48,49]

4.2 Rising healthcare costs

With the increasing prevalence of ticks and LD, hospitals are faced with the responsibility of treating a larger number of patients.[50] Although the quality and extent of care are undoubtedly important, the financial aspect of treating severe cases of LD cannot be overlooked. The management of severe LD necessitates more intensive care, resulting in higher costs.

In a case study conducted in Michigan, the incidence of LD has shown a significant increase of five times between 2000 and 2014. As a result, the estimated cost of LD to the healthcare system in Michigan was approximately $7.8 million in 2018. Additionally, there was a loss of $0.1 million USD in wages due to sick days caused by LD.[51] Although these figures may seem relatively small when compared to the financial impact of other climate-sensitive events such as the Washington wildfires or Hurricane Sandy, LD still imposes a considerable burden on outpatient services and incurs millions of dollars in public expenses annually. Within the hospital setting, around half of the total LD costs can be attributed to in-patient expenses, indicating that the cases requiring hospitalization demand more extensive treatment, attention, time, and care.[52]

5. Improvements

Locating relevant cases for this case-study-driven paper presented a significant challenge. It is worth noting that the majority of LD-related cases, studies, and epidemiological reports have a strong focus on the United States. This US-centric approach limits the availability of geographically diverse literature on LD, which is crucial for developing a comprehensive understanding of the current state of LD. In Asia, specifically, there is a noticeable lack of such literature, further hindering the construction of an accurate understanding of LD.[53] This gap is worsened by China's lack of a national database, making accurate data collection even more difficult. Considering that different regions may experience varying symptoms from different strains of LD, it is imperative to enhance the study and recognition of LD by publishing and disseminating more studies from Asian and South American regions to researchers worldwide.[22,54]

The relative lack of English-written papers from South America gives rise to a parallel concern. This language barrier, stemming from a substantial number of papers being written in Spanish, presents a twofold challenge. Firstly, it restricts the accessibility of these valuable contributions to a wider international audience. Secondly, it effectively necessitates that South American researchers possess fluency in both Spanish and English.[55] In order to foster greater dissemination of LD knowledge, it is advisable for journals or institutions to proactively offer translators to South American researchers.

Previously, it has been established that the inability of physicians to identify LD has resulted in a significant underreporting of cases and has posed challenges in accurately monitoring the geographic and temporal spread of the disease. The absence of case recognition has directly contributed to a decline in the number of reported cases, as indicated by the preponderance of epidemiological and region-wide case studies in South America over individual patient case studies. This issue is particularly significant due to the varying symptoms of LD in different regions, as discussed earlier. The scarcity of patient case studies hampers the identification of LD, as the characteristic symptoms of the disease are often misattributed. Moving forward, it is imperative to promote the recognition of region-specific LD by conducting more studies on cases specific to each region and allocating additional funding for the publication of case reports, particularly in South America and Asia.

Discussion

The incidence of LD has witnessed an upward trajectory, extending its reach to previously uncharted territories in recent times. Numerous pivotal elements have played a role in this pattern, encompassing heightened human proximity to carriers of LD, enhanced awareness and diagnostic measures, and the expansion of favorable tick habitats owing to climate fluctuations. This research underscores the significance of comprehending LD as a consequence of our capacity to monitor and identify it.

Urbanization has resulted in communities being in closer proximity to ticks and other carriers of LD, yet our awareness and understanding of the disease have often been delayed. Attempts have been made to tackle this problem by gathering information through citizen science projects and expanding the availability of serologic testing. However, in numerous regions where access to such resources and adequate medical training is lacking, the scarcity of data remains a significant obstacle. This gap is evident in the limited amount of non-US epidemiological research on LD and the insufficient knowledge of culturing and serologic testing procedures for specific strains of LD found outside the United States. With a greater amount of data, authorities can pinpoint areas with a high prevalence of LD and take appropriate measures to provide healthcare workers with training in recognizing the disease, as well as promote the use of more efficient testing methods.

With the growth in LD cases, which is further compounded by the impacts of climate change, there is a commensurate increase in unfavorable health outcomes and healthcare expenditures. Hence, it is crucial for healthcare professionals and public health authorities to work together to alleviate these burdens and obtain comprehensive data. Considering the growing challenges in collecting field data, proactive measures need to be implemented soon to avert more severe health outcomes and escalating costs in the coming years.

It is our conviction that by intensifying surveillance and acknowledgment of LD within the community, the quality of care for individuals affected by the disease will be enhanced. Furthermore, this approach will provide valuable insights for public health strategies and facilitate the acquisition of funding for additional research dissemination on LD. Given the expansion of the disease into previously unaffected areas and the rising number of cases in various communities, it is imperative to prioritize the sharing of research findings and the promotion of clinical recognition. However, these crucial steps can only be effectively undertaken after collecting comprehensive epidemiological and genetic data on LD.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Lyme Disease: LD;

Coronavirus disease 2019: COVID-19;

severe acute respiratory syndrome coronavirus 2: SARS-CoV-2.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

References

1. Ross Russell AL, Dryden MS, Pinto AA, Lovett JK. Lyme disease: diagnosis and management. Practical Neurol. 2018;18(6):455-64. doi:10.1136/practneurol-2018-001998 PMid:30282764
2. Schoen RT. Lyme disease. Curr Opin Rheumatol. 2020;32(3):1. doi:10.1097/BOR.0000000000000698 PMid:32141956
3. Arvikar SL, Steere AC. Diagnosis and Treatment of Lyme Arthritis. Infect Dis Clin North Am. 2015;29(2):269-80. doi:10.1016/j.idc.2015.02.004 PMid:25999223 PMCid:PMC4443866
4. Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis. JAMA. 2016; 315(16):1767. doi:10.1001/jama.2016.2884 PMid:27115378 PMCid:PMC7758915
5. Bush LM, Vazquez-Pertejo MT. Tick borne illness-Lyme disease. Dis Mon. 2018;64(5):195-212. doi:10.1016/j.disamonth.2018.01.007 PMid:29402399
6. Płusa T. History of the study, epidemiology of the disease and characterization of Borrelia burgdorferi infection. Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego. 2017;43(255): 99-103.
7. Ozdenerol E. GIS and Remote Sensing Use in the Exploration of Lyme Disease Epidemiology. Int J Environ Res Public Health. 2015;12(12): 15182-203. doi:10.3390/ijerph121214971 PMid:26633445 PMCid:PMC4690907
8. Boulanger N, Boyer P, Talagrand-Reboul E, Hansmann Y. Ticks and tick-borne diseases. Médecine et Maladies Infectieuses. 2019;49(2):87-97. doi:10.1016/j.medmal.2019.01.007 PMid:30736991
9. Stone BL, Tourand Y, Brissette CA. Brave New Worlds: The Expanding Universe of Lyme Disease. Vector Borne Zoonotic Dis. 2017;17(9):619-29. doi:10.1089/vbz.2017.2127 PMid:28727515 PMCid:PMC5576071
10. Zheng W, Chen H, Liu X, Guo X, Fu R. Severe Tick Infestation in a Hare and Potential Risk for Transmitting Pathogens to Humans. Korean J Parasitol. 2011;49(4):419-9. doi:10.3347/kjp.2011.49.4.419 PMid:22355211 PMCid:PMC3279682
11. Cunningham AA, Daszak P, Wood JLN. One Health, emerging infectious diseases and wildlife: two decades of progress? Philosophical transactions of the Royal Society of London Series B, Biological Sci. 2017;372(1725):20160167. doi:10.1098/rstb.2016.0167 PMid:28584175 PMCid:PMC5468692
12. Frank C. Mapping Lyme Disease Incidence for Diagnostic and Preventive Decisions, Maryland. Emerg Infect Dis. 2002;8(4):427-9. doi:10.3201/eid0804.000413 PMid:11971779 PMCid:PMC2730243
13. Aucott JN, Wang L, Yang T, Marsteller JA, Murphy SM, Uriyo M, et al. Incidence of Lyme Disease Diagnosis in a Maryland Medicaid Population, 2004-2011. Am J Epidemiol. 2018;187 (10):2202-9. doi:10.1093/aje/kwy133 PMid:29955850
14. Schwartz BS, Hofmeister EK, Glass GE, Arthur RR, Childs JE, Cranfield M. Lyme borreliosis in an inner-city park in Baltimore. Am J Public Health. 1991 doi:10.2105/AJPH.81.6.803 PMid:2029058 PMCid:PMC1405150
15. Borecka A, Małgorzata Szczypek, Pabin A, Kowalczuk K, Ewelina Maculewicz. Impact of tick-borne pathogens on the health risk of soldiers. Ann Agric Environ Med. 2023;30(2):211-6. doi:10.26444/aaem/159702 PMid:37387368
16. Clark IA. Chronic cerebral aspects of long COVID, post-stroke syndromes and similar states share their pathogenesis and perispinal etanercept treatment logic. Pharmacol Res Perspect. 2022;10(2). doi:10.1002/prp2.926 PMid:35174650 PMCid:PMC8850677
17. Brissett S, Myint KT, Lopez Y, Raiszadeh F, Sivapalan V, Kurian D. A curious case of Lyme carditis in an urban hospital. IDCases. 2021; 25:e01179. doi:10.1016/j.idcr.2021.e01179 PMid:34194998 PMCid:PMC8225969
18. O'Connell S. Lyme disease: a review. Commun Dis Rep CDR Rev. 1993;3(8):R111-115.
19. Guo L, Di L, Zhang C, Lin L, Di Y. Influence of urban expansion on Lyme disease risk: A case study in the U.S. I-95 Northeastern corridor. Cities. 2022;125:103633. doi:10.1016/j.cities.2022.103633
20. Semenza JC, Rocklöv J, Ebi KL. Climate Change and Cascading Risks from Infectious Disease. Infect Dis Ther. 2022 doi:10.1289/isee.2022.O-SY-044
21. Steere AC. Lyme disease: a growing threat to urban populations. Proc Natl Acad Sci. 1994; 91 (7): 2378-83. doi:10.1073/pnas.91.7.2378 PMid:8146126 PMCid:PMC43375
22. Carranza-Tamayo CO, Costa JNG da, Bastos WM. Lyme disease in the state of Tocantins, Brazil: report of the first cases. Braz J Infect Dis. 2012;16(6):586-9. doi:10.1016/j.bjid.2012.07.013 PMid:23141972
23. McNerney R. Diagnostics for Developing Countries. Diagnostics. 2015;5(2):200-9. doi:10.3390/diagnostics5020200 PMid:26854149 PMCid:PMC4665590
24. Stricker R, Johnson L. Lyme disease: the promise of Big Data, companion diagnostics and precision medicine. Infect Drug Resist. 2016;9:215-9. doi:10.2147/IDR.S114770 PMid:27672336 PMCid:PMC5024771
25. Kobayashi T, Auwaerter PG. Diagnostic Testing for Lyme Disease. Infect Dis Clin North Am. 2022;36 (3):605-20. doi:10.1016/j.idc.2022.04.001 PMid:36116838
26. Waddell LA, Greig J, Mascarenhas M, Harding S, Lindsay R, Ogden N. The Accuracy of Diagnostic Tests for Lyme Disease in Humans, A Systematic Review and Meta-Analysis of North American Research. Stevenson B, editor. PLOS One. 2016;11 (12):e0168613. doi:10.1371/journal.pone.0168613 PMid:28002488 PMCid:PMC5176185
27. Cook M, Puri B. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med. 2016;9: 427-40. doi:10.2147/IJGM.S122313 PMid:27920571 PMCid:PMC5125990
28. Strickland G Thomas, Karp Andrea C, Mathews A, Peña César A. Utilization and Cost of Serologic Tests for Lyme Disease in Maryland. J Infect Dis. 1997;176(3):819-21. doi:10.1086/517311 PMid:9291343
29. Moore A, Nelson C, Molins C, Mead P, Schriefer M. Current Guidelines, Common Clinical Pitfalls, and Future Directions for Laboratory Diagnosis of Lyme Disease, United States. Emerg Infect Dis . 2016;22(7). doi:10.3201/2207.151694
30. Johnston B, Conly J. Lyme Disease: Is It or Is It Not? Canadian J Infectious Dis Med Microbiol. 2005;16(6):325-8. doi:10.1155/2005/278304 PMid:18159514 PMCid:PMC2094998
31. Bobe JR, Jutras BL, Horn EJ, Embers ME, Bailey A, Moritz RL, et al. Recent Progress in Lyme Disease and Remaining Challenges. Front Med. 2021;8. doi:10.3389/fmed.2021.666554 PMid:34485323

PMCid:PMC8416313
32. Marques AR. Laboratory Diagnosis of Lyme Disease. Infect Dis Clin North Am. 2015;29(2):295-307. doi:10.1016/j.idc.2015.02.005 PMid:25999225 PMCid:PMC4441761
33. Combs M, Tufts DM, Adams B, Lin YP, Sergios-Orestis Kolokotronis, Diuk-Wasser MA. Host adaptation drives genetic diversity in a vector-borne disease system. PNAS Nexus. 2023;2(8). doi:10.1093/pnasnexus/pgad234 PMid:37559749 PMCid:PMC10408703
34. Brisson D, Drecktrah D, Eggers CH, Samuels DS. Genetics of Borrelia burgdorferi. Ann Rev Genet. 2012;46(1): 515-36 doi:10.1146/annurev-genet-011112-112140 PMid:22974303 PMCid:PMC3856702
35. Stobierski MG, Hall WN, Robinson-Dunn B, Stiefel H, Shiflett S, Carlson V. Isolation of Borrelia burgdorferi from Two Patients in Michigan. Clin Infect Dis. 1994;19(5):944-6. doi:10.1093/clinids/19.5.944 PMid:7893885
36. Mattoon S, Baumhart C, Barsallo Cochez AC, MacQueen D, Snedeker J, Yancey CB, et al. Primary care clinical provider knowledge and experiences in the diagnosis and treatment of tick-borne illness: a qualitative assessment from a Lyme disease endemic community. BMC Infect Dis. 2021;21(1). doi:10.1186/s12879-021-06622-6 PMid:34465298 PMCid:PMC8408947
37. Johnson LB, Maloney EL. Access to Care in Lyme Disease: Clinician Barriers to Providing Care. Healthcare. 2022; 10 (10): 1882. doi:10.3390/healthcare10101882 PMid:36292329 PMCid:PMC9601439
38. Natalino Hajime Yoshinari, Lucia V, Bonin S, Falkingham E, Trevisan G. The Current State of Knowledge on Baggio-Yoshinari Syndrome (Brazilian Lyme Disease-like Illness): Chronological Presentation of Historical and Scientific Events Observed over the Last 30 Years. Pathogens. 2022;11(8):889-9. doi:10.3390/pathogens11080889 PMid:36015013 PMCid:PMC9415174
39. Godoy RE, de Santana ALF, Graser C, Rangel EF, Vilela ML. Aspects on the Ecology of Phlebotomine Sand Flies (Diptera: Psychodidae) From Guaraí, State of Tocantins, Brazil, Endemic Area for American Cutaneous Leishmaniasis. J Med Entomol. 2016;54(1):229-35. doi:10.1093/jme/tjw148 PMid:28082651
40. Thiago Fernandes Martins, Mariana Granziera Spolidorio, Alves C, Iza, Natalino Hajime Yoshinari, Labruna MB. Ocorrência de carrapatos (Acari: Ixodidae) no município de Goiatins, Tocantins. Revista Brasileira De Parasitologia Veterinaria. 2009;18(02):50-2 doi:10.4322/rbpv.01802011 PMid:19602318
41. Gouveia EA, Alves MF, Mantovani E, Oyafuso LK, Bonoldi VLN, Yoshinari NH. Profile of patients with Baggio-Yoshinari Syndrome admitted at "Instituto de Infectologia Emilio Ribas." Revista do Instituto de Medicina Tropical de Sao Paulo. 2010;52(6):297-303. doi:10.1590/S0036-46652010000600003 PMid:21225212
42. Lantos PM. Chronic Lyme Disease. Infect Dis Clin North Am. 2015; 29(2):325-40. doi:10.1016/j.idc.2015.02.006 PMid:25999227 PMCid:PMC4477530
43. Aucott J, Morrison C, Munoz B, Rowe PC, Schwarzwalder A, West SK. Diagnostic challenges of early Lyme disease: Lessons from a community case series. BMC Infect Dis. 2009; 9(1). doi:10.1186/1471-2334-9-79 PMid:19486523 PMCid:PMC2698836
44. Millins C, Gilbert L, Medlock J, Hansford K, Thompson DB, Biek R. Effects of conservation management of landscapes and vertebrate communities on Lyme borreliosis risk in the United Kingdom. Philos Trans R Soc Lond B Biol Sci 2017;372(1722). doi:10.1098/rstb.2016.0123 PMid:28438912 PMCid:PMC5413871
45. Salomon J, Hamer SA, Swei A. A Beginner's Guide to Collecting Questing Hard Ticks (Acari: Ixodidae): A Standardized Tick Dragging Protocol. Machtinger E, editor. J Insect Sci. 2020;20 (6). doi:10.1093/jisesa/ieaa073 PMid:33135760 PMCid:PMC7604844
46. Bouchard C, Leonard E, Koffi JK, Pelcat Y, Peregrine A, Chilton N, et al. The increasing risk of Lyme disease in Canada. Can Vet J. 2015;56 (7):693-9.
47. Lewis J, Boudreau C, Patterson J, Bradet-Legris J, Lloyd V. Citizen Science and Community Engagement in Tick Surveillance-A Canadian Case Study. Healthcare. 2018;6(1):22. doi:10.3390/healthcare6010022 PMid:29498648 PMCid:PMC5872229
48. Kluger J. How Climate Change Affects the Spread of Lyme Disease. Time. 2023 [cited 2023 Sep 7]. Available from: https://time.com/6262408/climate-change-lyme-disease-ticks/#:~:text=It%27s%20true%20that%20the%20ticks
49. Brownstein JS, Holford TR, Fish D. Effect of Climate Change on Lyme Disease Risk in North America. EcoHealth. 2005;2(1):38-46. doi:10.1007/s10393-004-0139-x PMid:19008966 PMCid:PMC2582486
50. Schwartz AM, Shankar MB, Kugeler KJ, Max RJ, Hinckley AF, Meltzer MI, et al. Epidemiology and cost of Lyme disease-related hospitalizations among patients with employer-sponsored health insurance-United States, 2005-2014. Zoonoses Public Health. 2020;67 (4):407-15. doi:10.1111/zph.12699 PMid:32462811 PMCid:PMC7521202
51. Limaye VS, Max W, Constible J, Knowlton K. Estimating the Health-Related Costs of 10 Climate-Sensitive U.S. Events During 2012. GeoHealth. 2019;3(9):245-65. doi:10.1029/2019GH000202 PMid:32159045 PMCid:PMC7007172
52. Hook SA, Jeon S, Niesobecki SA, Hansen AP, Meek JI, Bjork JK, Dorr FM, Rutz HJ, Feldman KA, White JL, Backenson PB. Economic burden of reported lyme disease in high-incidence areas, United States, 2014–2016. Emerg Infect Dis. 2022;28(6):1170. doi:10.3201/eid2806.211335
53. Stark JH, Li X, Zhang JC, Burn L, Valluri SR, Liang J, et al. Systematic Review and Meta-analysis of Lyme Disease Data and Seropositivity for Borrelia burgdorferi, China, 2005-2020. Emerg Infect Dis. 2022;28 (12):2389. doi:10.3201/eid2812.212612 PMid:36417925 PMCid:PMC9707590
54. Liveris D, Varde S, Iyer R, Koenig S, Bittker S, Cooper D, et al. Genetic Diversity of Borrelia burgdorferi in Lyme Disease Patients as Determined by Culture versus Direct PCR with Clinical Specimens. J Clin Microbiol. 1999;37(3):565-9. doi:10.1128/JCM.37.3.565-569.1999 PMid:9986813 PMCid:PMC84470
55. Ramírez-Castañeda V. Disadvantages in preparing and publishing scientific papers caused by the dominance of the English language in science: The case of Colombian researchers in biological sciences. Manalo E, editor. PLOS One. 2020;15(9):e0238372. doi:10.1371/journal.pone.0238372 PMid:32936821 PMCid:PMC7494110

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