Zoonoses and Public Health

WILEY

SHORT COMMUNICATION

Pregnancy Among Reported Lyme Disease Cases—United States, 1992–2019

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Received: 24 July 2024 | **Revised:** 13 September 2024 | **Accepted:** 14 September 2024

Funding: This study was funded by the U.S. Centers for Disease Control and Prevention.

Keywords: *Borrelia burgdorferi* | Lyme disease | pregnancy | surveillance

ABSTRACT

Background: Lyme disease (LD), the most common vector-borne disease in the United States, typically presents with a localised erythema migrans rash (EM). Left untreated, infection can disseminate to cause severe heart, joint or nervous system manifestations. Summaries of LD surveillance data have been published previously but did not include the frequency, demographic or clinical characteristics of LD cases during pregnancy.

Methods: We summarised confirmed and probable LD cases by pregnancy status as reported to the U.S. Centers for Disease Control and Prevention during 1992–2019. We defined an LD case during pregnancy as one with (1) female sex, (2) age 14–49 years and (3) positive pregnancy indication. We evaluated the frequency, seasonality, age distribution, race and ethnicity, geographic distribution and clinical manifestations of LD cases during pregnancy and cases among non-pregnant females. We compared proportions using chi-squared tests.

Results: Among 698,876 reported LD cases, 112,002 (16%) were confirmed or probable cases among females aged 14–49 years; 32,301 (29%) were specifically reported as non-pregnant and 643 (0.6%) (568 confirmed and 75 probable cases) reported as pregnant. Illness onset peaked in June among LD cases during pregnancy, but in July for cases among non-pregnant females. A higher proportion of confirmed LD cases during pregnancy had only EM rash than did cases among non-pregnant females (66% vs. 60%, $p = 0.019$).

Conclusions: LD cases during pregnancy are rare. Compared to non-pregnant females, cases among pregnant females more commonly involve early clinical manifestations. These patterns could suggest earlier detection or more complete reporting of LD cases during pregnancy than their non-pregnant counterparts. Earlier detection could be due to frequent contact with healthcare or increased self-advocacy during pregnancy. Prompt antimicrobial treatment is critical for preventing severe disease and reducing risk of adverse pregnancy or birth outcomes.

1 | Introduction

In the United States, Lyme disease (LD) is the most common vector-borne disease, but is geographically focal, with >90% of cases reported from the Northeast, mid-Atlantic and upper-Midwest (CDC 2019). Since national public health surveillance was initiated in the early 1990s, the geographic area with risk of LD has expanded and the number of cases reported annually has increased from less than 10,000 to >40,000 (Kugeler et al. 2015; Schwartz et al. 2017). LD is caused by certain

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Summary

- Information on Lyme disease (LD) cases during pregnancy is limited; we summarise characteristics of LD cases during pregnancy in the United States reported through surveillance during 1992–2019.
- LD during pregnancy is rare, accounting for ~0.1% of reported cases. Compared to cases among non-pregnant females, cases among pregnant females are more likely limited to early clinical manifestations. Nevertheless, up to a third of reported cases in pregnant women include clinical evidence of disseminated infection.
- Educating healthcare providers regarding the frequency, diagnosis and treatment of LD cases during pregnancy is important to mitigate risk of adverse birth outcomes.

genospecies of *Borrelia burgdorferi* sensu lato and transmitted through the bite of infected blacklegged ticks (Pritt et al. 2016). For most people, LD presents with a red, expanding rash called erythema migrans (EM), that may be accompanied by general symptoms such as arthralgia and malaise. Early diagnosis and treatment can mitigate longer term effects of infection; untreated infection can disseminate to the heart, joints or nervous system and cause more severe disease (CDC 2022; Mead 2022).

The epidemiology of LD, as elucidated through public health surveillance, demonstrates a male predominance and bimodal age distribution with incidence peaks among children 5–14 years of age and older adults (Mead 2022). Previous published summaries of LD surveillance data have lacked data regarding pregnancy (Bacon, Kugeler, and Mead 2008; Schwartz et al. 2017). There is limited information on how commonly LD occurs among pregnant females in the United States and if the characteristics of LD during pregnancy differ from LD in non-pregnant females. Here, we summarise LD surveillance data as reported to the U.S. Centers for Disease Control and Prevention (CDC) during 1992–2019 according to pregnancy status.

2 | Methods

2.1 | Data Source and Surveillance Case Definitions

In accordance with legal mandates and surveillance practices, states and local health departments voluntarily report LD cases to CDC through the Nationally Notifiable Diseases Surveillance System (NNDSS). Data elements that accompany LD case reports include case status (i.e., confirmed and probable), patient demographics (e.g., age, sex, race and ethnicity), state and county of residence, date of illness onset or diagnosis and optional clinical information (e.g., clinical symptoms and pregnancy status). Data completeness varies by reporting state and over time. As this study involves secondary data analyses of de-identified surveillance data, CDC determined that it does not involve human subjects and requires no additional review.

Standardised surveillance case definitions, as created and approved by the U.S. Council of State and Territorial Epidemiologists (CSTE), have been used since national surveillance for LD began (CDC 2021). During 1992–2007, surveillance included confirmed cases only. In brief, confirmed cases were defined as those with EM or those with laboratory evidence of infection and ≥1 specific clinical manifestation indicating disseminated infection. Starting in 2008, laboratory evidence of infection was more specifically elucidated and a probable case definition was added. A 2017 update to the case definition introduced differential criteria based on the prior probability of exposure, increasing specificity in states with <10 confirmed LD cases per 100,000 population (CDC 2021).

2.2 | Analysis

We examined the frequency overall and per year, age distribution, race and ethnicity, geographic distribution, seasonality and clinical manifestations of LD cases as reported to CDC during 1992–2019 according to pregnancy status. We defined an LD case during pregnancy as one with all the following criteria as reported by the jurisdiction of residence: (1) female sex, (2) age 14–49 years, and (3) positive pregnancy indication. We compared characteristics of confirmed and probable LD cases during pregnancy to those of confirmed and probable cases among females aged 14–49 years with specific negative pregnancy indication. However, to compare clinical manifestations, we only used data for confirmed cases since clinical manifestation data are only available for that classification. Chi-squared tests were used to compare clinical manifestation proportions; a p value ≤ 0.05 was considered statistically significant. For geographic analyses, states were classified into one of three categories based on LD risk: 'high incidence', 'low incidence' and 'neighbouring' (Kwit et al. 2018; Schwartz et al. 2017).[1]

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). This activity was reviewed by CDC and deemed non-research.

3 | Results

Among 698,876 LD cases reported to CDC during 1992–2019, 112,002 (16.0%) were among females aged 14–49 years. Of these, 32,944 (29.4%) had pregnancy status indicated: 32,301 (28.8%; 27,127 confirmed and 5174 probable) were reported as non-pregnant and 643 (0.6%; 568 confirmed and 75 probable cases) were reported as pregnant.

The 3-year moving average of LD cases during pregnancy mirrored that among all reported LD cases during the same time frame (Figure 1). A mean of 23 confirmed and probable LD cases during pregnancy were reported annually during 1992–2019 (minimum: 4 in 1992; maximum: 38 in 2017).

3.1 | Demographics

The median patient age among LD cases during pregnancy was 30 years (interquartile range [IQR]: 26–35 years), as compared to

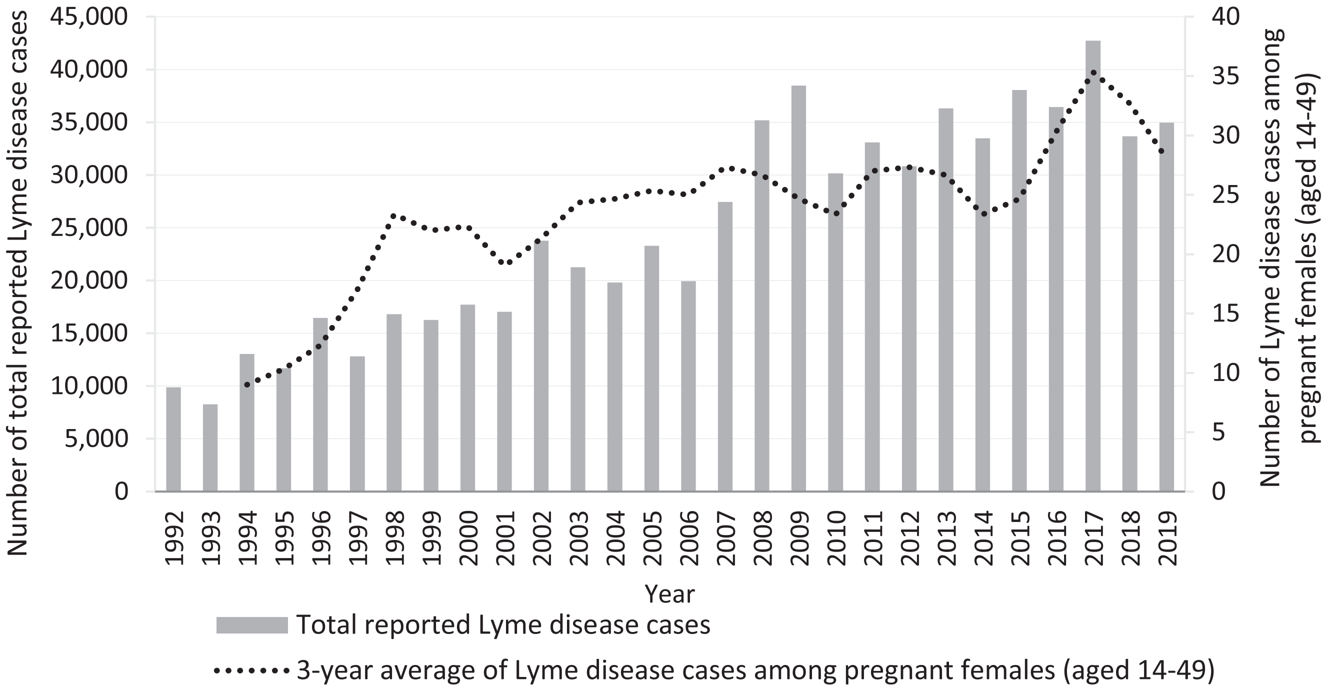

FIGURE 1 | Number of total Lyme disease cases reported per year overall and among pregnant females aged 14–49 years—United States, 1992—2019. Standardised surveillance case definitions include confirmed and probable cases (https://ndc.services.cdc.gov/conditions/lyme-disease/).

a median of 36 years (IQR: 25–44 years) for cases among non-pregnant females aged 14–49 years. White patients ($n=430$) accounted for 67% of cases during pregnancy, followed by unknown race ($n=152$, 24%), Other ($n=25$, 4%), Asian/Pacific Islander ($n=13$, 2%), Hispanic ($n=11$, 2%), Black ($n=9$, 1%) and Native American/Alaska Native ($n=3$, <1%). The race and ethnicity distribution among LD cases during pregnancy was comparable to cases among non-pregnant females (Table 1).

3.2 | Geography

During 1992–2019, 585 (91%) of 643 LD cases during pregnancy were among residents of high-incidence states, 6% were among residents of neighbouring states and 3% among residents of low-incidence states, a distribution comparable to cases among non-pregnant females (Table 1).

3.3 | Seasonality

Illness onset among LD cases was most common during the summer months, regardless of pregnancy status (Figure 2). LD cases during pregnancy more commonly had illness onset in June (32%), whereas cases among non-pregnant females more commonly had illness onset in July (25%).

3.4 | Clinical Manifestations

Among the 27,695 LD cases among females aged 14–49 years that were confirmed, 24,241 (88%) had ≥1 clinical manifestation reported; 496 (2%) were pregnant and 23,745 (98%) non-pregnant (Table 2).

EM rash was noted in 79% of cases during pregnancy and 74% of cases among non-pregnant females. An EM rash only, with no other disseminated manifestations, occurred among 66% of LD cases during pregnancy and 60% of cases among non-pregnant females ($p=0.019$) (Table 2). Age, race and ethnicity distributions for specific clinical manifestations did not differ by pregnancy status (data not shown).

4 | Discussion

Among 698,876 LD cases reported during 28 years of public health surveillance, we identified 643 (0.06%) during pregnancy. LD cases during pregnancy more commonly presented with EM rash only and might have had illness onset somewhat earlier in the summers than cases among non-pregnant females. This pattern of earlier disease detection might reflect increased awareness of general health during pregnancy and consequent early healthcare-seeking behaviour as compared to the general public (Lambert 2020). It may also reflect more complete provider reporting of LD cases during pregnancy, as EM rashes are the most common and most often underreported form of the disease (Cartter et al. 2018; Ertel, Nelson, and Cartter 2012; White et al. 2018). Nevertheless, disseminated symptoms were also reported for approximately one third of LD cases during pregnancy, suggesting some cases might experience delays in treatment and increased potential for complications or risk of adverse birth outcomes.

Transplacental transmission of non-LD *Borrelia* strains, such as *B. hermsii*, a cause of soft tick relapsing fever,[2] has been documented (Lawaczeck et al. 2012; Moro et al. 2001). Early reports of untreated LD cases during pregnancy suggest that *B. burgdorferi* might affect the placenta and possibly be transmitted to

TABLE 1 | Characteristics of total reported Lyme disease cases among females aged 14–49 by pregnancy status—United States, 1992–2019.[a,b]

Characteristics	Reported Lyme disease cases among females aged 14–49 years			
	Pregnant (n = 643)	Not pregnant (n = 32,301)	Unknown/missing pregnancy status (n = 79,058)	Total (n = 112,002)
Age (years)				
14–19	39 (6.1)	4934 (15.3)	11,793 (14.9)	16,766
20–25	118 (18.4)	3508 (10.9)	9319 (11.8)	12,945
26–31	206 (32.0)	3861 (12.0)	10,286 (13.0)	14,353
32–37	186 (28.9)	5234 (16.2)	13,585 (17.2)	19,005
38–43	74 (11.5)	6594 (20.4)	15,904 (20.1)	22,572
44–49	20 (3.1)	8170 (25.3)	18,171 (23.0)	26,361
Race				
White	430 (66.9)	20,788 (64.4)	40,305 (51.0)	61,523
Black	9 (1.4)	570 (1.8)	1278 (1.6)	1857
Asian/Pacific Islander	13 (2.0)	316 (1.0)	841 (1.1)	1170
Native American/ Alaskan Native	3 (0.5)	76 (0.2)	365 (0.5)	444
Hispanic	11 (1.7)	570 (1.8)	1885 (2.4)	2466
Other	25 (3.9)	1428 (4.4)	1856 (2.4)	3309
Unknown	152 (23.6)	8553 (26.5)	32,528 (41.1)	41,233
Case status[a]				
Confirmed	568 (88.3)	27,127 (84.0)	65,691 (83.1)	93,386
Probable	75 (11.7)	5174 (16.0)	13,367 (16.9)	18,616
State categories[b]				
High-incidence	585 (91.0)	29,388 (91.0)	73,841 (93.4)	103,814
Neighbouring	36 (5.6)	2007 (6.2)	1901 (2.4)	3944
Low-incidence	22 (3.4)	906 (2.8)	3316 (4.2)	4244

[a]States and local health departments voluntarily report Lyme disease cases to U.S. Centers for Disease Control and Prevention through the Nationally Notifiable Diseases Surveillance System. During 1992–2007, surveillance included confirmed cases only (https://ndc.services.cdc.gov/conditions/lyme-disease/).
[b]States with an incidence of ≥ 10 confirmed Lyme disease cases per 100,000 population for any three reporting years were categorised as high incidence. Annual incidence rates per 100,000 population were calculated by state using mid-year U.S. Census Bureau estimates from 2019 (https://www.census.gov/). In addition to the District of Columbia, 15 states in the Northeast, mid-Atlantic, and upper Midwest met this criterion: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia and Wisconsin. States with a shared border to any of the high-incidence states or that were located between high-incidence areas were categorised as neighbouring; these 10 states were Illinois, Indiana, Iowa, Kentucky, Michigan, North Carolina, North Dakota, Ohio, South Dakota and Tennessee. All other states were categorised as low incidence.

the developing child (CDC 1985). In a systematic review of the impact of gestational LD in humans on the fetus and newborn from 1969 to 2017, 45 relevant articles were identified[3] and highlighted the lower rate of adverse birth outcomes among females treated for LD during their pregnancy compared to those who were not (Waddell et al. 2018). Additionally, studies in both animals and humans have suggested that factors during pregnancy, including increased progesterone or interleukin-4 production, may decrease the severity of LD (Maraspin et al. 2020; Moro et al. 2001; Schlesinger et al. 1985).

This analysis is subject to limitations. First, the frequency denoted here reflects the minimum number of LD cases during pregnancy in the United States during this period. Given the small number of pregnant cases, statistical comparisons for some case characteristics (e.g., month of onset) were not always feasible or appropriate. Underreporting is well-documented with LD surveillance, particularly for early disease characterised by EM rash (White et al. 2018). Rare diseases are more commonly reported to public health (Cartter et al. 2018; Ertel, Nelson, and Cartter 2012); this might extend to include a common disease under unique or more vulnerable circumstances, such as pregnancy. Additionally, errors in electronic data transmission might have excluded some pregnant females from analysis—71% of records for females aged 14–49 had missing pregnancy status and 65 males and 131 females of non-childbearing age were also denoted as pregnant, including in one state in 1 year where 29 records of LD among ‘pregnant males’ were transmitted to CDC,

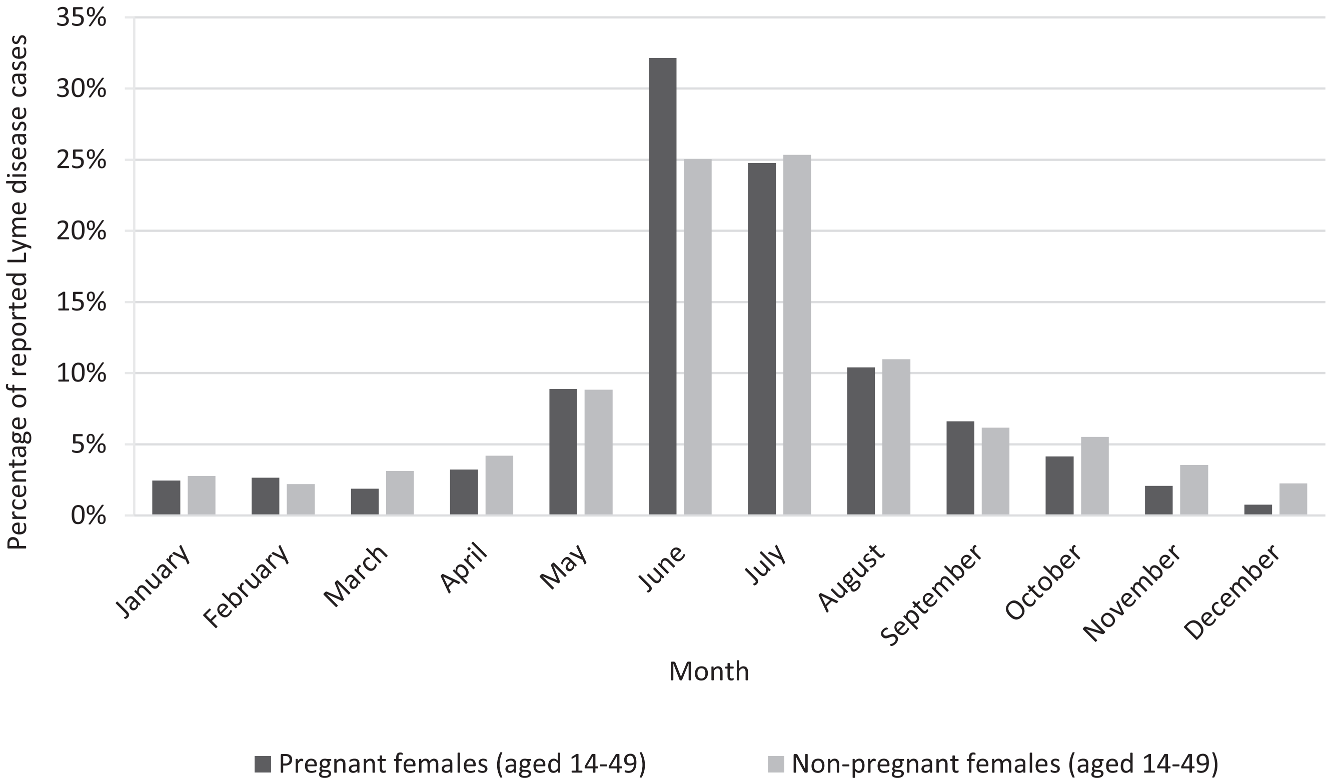

FIGURE 2 | Percentage of reported Lyme disease cases among females aged 14–49 by pregnancy status and month of illness onset—United States, 1992–2019. Illness onset was unknown for 18% of pregnant females aged 14–49 years and 17% non-pregnant females aged 14–49 years.

TABLE 2 | Clinical manifestations reported for confirmed Lyme disease cases of among females aged 14–49 by pregnancy status, 1992–2019.[a,b]

Clinical manifestations[*,c]	Pregnant females ($n=496$)	Non-pregnant females ($n=23,745$)
Erythema migrans (EM) only	328 (66%)	14,331 (60%)
EM with disseminated manifestations	65 (13%)	3240 (14%)
Disseminated manifestations only	103 (21%)	6174 (26%)

[a]Standardised surveillance case definitions include confirmed and probable cases (https://ndc.services.cdc.gov/conditions/lyme-disease/). Clinical manifestation data are only available for confirmed cases.
[b]Clinical manifestations were unknown for 72 (12.7%) pregnant females and 3382 (12.5%) of non-pregnant females.
[c]Disseminated manifestations include arthritis, facial palsy, encephalitis/encephalomyelitis, radiculoneuropathy, lymphocytic meningitis and/or second or third degree atrioventricular block.
*Chi-squared test of clinical manifestations by pregnancy status, $p=0.019$.

illustrating the often challenging nature of electronic data transmission for a high-volume disease, particularly during the early years of national surveillance (1990s). Missing data in a binary pregnancy field might simply reflect a non-pregnant status for most cases (Schwartz et al. 2017). Secondly, the geographic distribution of cases during pregnancy generally reflects what is known regarding risk of LD but also reflects travel-associated infection. Cases reported from low-incidence states typically reflect travel to higher-incidence locations, as cases are reported according to residence not exposure (Forrester et al. 2015).

In the United States, reported LD cases during pregnancy are rare. Available data ascertained through decades of public health surveillance suggest that pregnant females might be diagnosed during early disease or reported to public health more completely than their non-pregnant counterparts. Public health surveillance data do not include detailed data on possible co-infections that might alter the pathogenic processes during pregnancy. These surveillance data also do not include prospective follow-up on LD cases during pregnancy and therefore lack details on pregnancy or birth outcomes. Other large data sources including appropriate control groups, should be used to evaluate those impacts. Prompt detection and treatment are important to mitigate more severe effects of LD, including during pregnancy (Moro et al. 2001; Schlesinger et al. 1985; Waddell et al. 2018). Public health should prioritise education of healthcare providers regarding epidemiology, diagnosis and treatment of LD cases during pregnancy. Pregnant persons who reside in or visit areas with a high risk for LD or areas where LD is spreading, should be vigilant regarding risk of LD and other tick-borne diseases and take steps to prevent tick exposures and seek care after a tick bite or when potential symptoms occur. In the absence of other effective and available prevention measures, wearing repellent, regularly using permethrin-treated clothing and performing regular tick checks after coming indoors are important prevention tools, regardless of pregnancy status.

Acknowledgements

We wish to thank the public health professionals who have investigated human Lyme disease cases and voluntarily reported them to CDC.

Ethics Statement

As this study involves secondary analyses of de-identified surveillance data, CDC determined that it does not involve human subjects and requires no additional review.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Endnotes

[1] States with an incidence of ≥ 10 confirmed LD cases per 100,000 population for any three reporting years were categorised as high incidence. Annual incidence rates per 100,000 population were calculated by state using mid-year U.S. Census Bureau estimates from 2019 (https://www.census.gov/). In addition to the District of Columbia, 15 states in the Northeast, mid-Atlantic and upper Midwest met this criterion: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia and Wisconsin. States with a shared border to any of the high-incidence states or that were located between high-incidence areas were categorised as neighbouring; these 10 states were Illinois, Indiana, Iowa, Kentucky, Michigan, North Carolina, North Dakota, Ohio, South Dakota and Tennessee. All other states were categorised as low incidence.

[2] Soft tick relapsing fever (STRF), previously known as tick-borne relapsing fever (TBRF).

[3] Thirty case reports/case series, nine cohort studies, four cross-sectional studies and two case–control studies were identified.

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