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Potential quantitative effect of a laboratory-based approach to Lyme disease surveillance in high-incidence states

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Abstract

Historically, public health surveillance for Lyme disease has required clinical follow-up on positive laboratory reports for the purpose of case classification. In areas with sustained high incidence of the disease, this resource-intensive activity yields a limited benefit to public health practice. A range of burden-reducing strategies have been implemented in many states, creating inconsistencies that limit the ability to decipher trends. Laboratory-based surveillance, or surveillance based solely on positive laboratory reports without follow-up for clinical information on positive laboratory reports, emerged as a feasible alternative to improve standardization in already high-incidence areas. To inform expectations of a laboratory-based surveillance model, we conducted a retrospective analysis of Lyme disease data collected during 2012–2018 from 10 high-incidence states. The number of individuals with laboratory evidence of infection ranged from 1302 to 20,994 per state and year. On average, 55% of those were ultimately classified as confirmed or probable cases (range: 29%–86%). Among all individuals with positive laboratory

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CONFLICT OF INTERESTS

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evidence, 18% (range: 2%–37%) were determined to be ‘not a case’ upon investigation and 23% (range: 2%–52%) were classified as suspect cases due to lack of associated clinical information and thus were not reported to the Centers for Disease Control and Prevention (CDC). The number of reported cases under a laboratory-based approach to surveillance in high-incidence states using recommended two-tier testing algorithms is likely to be, on average, 1.2 times higher (range: 0.6–1.8 times) than what was reported to CDC during 2012–2018. A laboratory-based surveillance approach for high-incidence states will improve standardization and reduce burden on public health systems, allowing public health resources to focus on prevention messaging, exploration of novel prevention strategies and alternative data sources to yield information on the epidemiology of Lyme disease.

Keywords

laboratory; Lyme disease; surveillance; two-tier testing

1 | INTRODUCTION

In the United States, Lyme disease, or Lyme borreliosis, is caused by the spirochetes *Borrelia burgdorferi* sensu stricto and the recently described *Borrelia mayonii* (Pritt et al., 2016; Steere, 2020). The tick-transmitted infection is geographically focal, occurring primarily in the north-eastern, mid-Atlantic and upper midwestern states. Nevertheless, Lyme disease is one of the most common of all notifiable infectious conditions nationwide, with 30,000–40,000 cases reported to the Centers for Disease Control and Prevention (CDC) each year (Schwartz et al., 2017).

National surveillance for Lyme disease began in the United States in 1991. Clinicians report possible cases to their local or state health departments and positive laboratory reports are transmitted from laboratories to health departments as per state regulations. Health department personnel evaluate these reports, obtain clinical information to accompany positive laboratory reports and classify cases according to a standardized case definition created and approved by the Council of State and Territorial Epidemiologists (CSTE) (Centers for Disease Control & Prevention, 2021b). In accordance with defined purposes of public health surveillance, surveillance for Lyme disease has yielded substantial information to describe the magnitude and geographic distribution, clinical features and demographics of persons most affected by Lyme disease (Schwartz et al., 2017). Over time, surveillance for Lyme disease has faced growing challenges, particularly in the most highly affected areas, where a large number of positive laboratory reports require extensive personnel resources to collect clinical information for the purpose of surveillance case classification (Cartter et al., 2018; Rutz et al., 2016). In areas with perennial high risk of Lyme disease, the mainstay of public health mitigation efforts is educational outreach about prevention methods; new case reports generally do not trigger additional specific public health action.

Although the purpose of case definitions is to create standards that ensure comparability of data across states, several jurisdictions have been unable to meet objectives and have made

adjustments that limit comparability of data collected across jurisdictions and over time (Lukacik et al., 2018; Rutz et al., 2016).

An alternative approach to surveillance that minimizes human resources, while also increasing the comparability of data collected across high-incidence states, relies on tracking positive laboratory reports with no active follow-up for associated clinical information. Here, we explore the potential quantitative effect of such an approach to surveillance using retrospective data. We describe patterns in laboratory reports and final reported case counts from states with a high incidence of Lyme disease during 2012–2018 and use those data to inform expectations for average reported case counts under two distinct laboratory-based approaches to surveillance.

2 | MATERIALS AND METHODS

Public health personnel from the 15 states with the highest average annual incidence of Lyme disease, all located in the northeast, mid-Atlantic and upper Midwest United States, were asked to participate in a retrospective review and analysis of laboratory data and reported Lyme disease cases captured in their surveillance systems during 2012–2018. These states were Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, Pennsylvania, New Hampshire, New Jersey, New York, Rhode Island, Virginia, Vermont, West Virginia and Wisconsin.

2.1 | Surveillance case definition and associated laboratory evidence of infection

Surveillance data queries identified case reports captured and classified under case definitions in effect during 2012–2018. Although the case definition was revised in 2017, the specific modification defined case classification criteria for low-incidence jurisdictions and did not impact surveillance practice or classification in high-incidence areas (Centers for Disease Control & Prevention, 2021a). In brief, a confirmed case of Lyme disease in established high-incidence areas was as follows: (a) an erythema migrans (EM) rash documented by a healthcare provider; or (b) laboratory evidence of infection accompanied by at least one defined clinical manifestation. A probable case was any other case of clinician-diagnosed Lyme disease with laboratory evidence of infection. Laboratory evidence of infection for surveillance purposes was defined as a positive culture or a positive serologic testing. Serologic positivity was either a two-tier IgM or IgG test, where the first tier was an enzyme immunoassay (EIA) or immunofluorescence assay (IFA), followed by a reflex immunoblot. Although not recommended to aid in patient diagnosis, a ‘single-tier’ IgG immunoblot absent a prior EIA was also sufficient laboratory evidence of infection for the purposes of surveillance.

Suspect cases in high-incidence jurisdictions had laboratory evidence of infection, without any associated clinical information. This occurs when follow-up to collect clinical information is attempted and unsuccessful, provider responses do not include sufficient information to appropriately classify cases or because follow-up was never attempted. Investigated reports can also be deemed ‘not a case’ after follow-up when there is no compatible illness or record of healthcare provider diagnosis of Lyme disease. Only confirmed and probable cases are reported to CDC.

2.2 | Data collection

Participating state health departments provided aggregate annual counts for several variables for analysis. Variables included the total number of individuals with laboratory evidence of infection each year in their surveillance system, the final surveillance case classification of those individuals (confirmed, probable, suspect, not a case), the final classification according to three serologic types of laboratory evidence of infection (two-tier IgM, two-tier IgG and single IgG immunoblot), demographics (sex and age) of persons with laboratory evidence of infection and demographics of persons that ended up in national tallies of confirmed and probable cases. Some jurisdictions provided data for only certain years, and some only for certain variables; these subjective decisions were made by individual jurisdictions based on knowledge of when surveillance practices may have rendered data incomparable to other years or when the variable could not be reliably extracted from the surveillance system. Some jurisdictions did not participate because their surveillance practices differed from other jurisdictions to a degree that precluded generalizable calculations using their data.

2.3 | Analysis

We summarized the mean, ranges and proportions across states and years for several variables. Means and proportions per state and year were averaged to obtain global figures and were not weighted by sample size; therefore, proportions provided by states with smaller populations factored the same into calculations as proportions provided by states with larger populations.

As laboratory reports could reflect provider-ordering practices as well as disease risk, we assessed the sex and age distribution of persons with laboratory evidence of infection and compared those to the demographic distribution of confirmed and probable cases reported from each state.

We calculated ratios under two scenarios of laboratory evidence of infection to describe how expected case counts from high-incidence states under a laboratory-only surveillance approach would differ from what was reported on average from high-incidence states during the years under study, 2012–2018. These scenarios were as follows: (A) total individuals with laboratory evidence of infection as described above in accordance with how data were classified during 2012–2018, and (B) modified laboratory evidence of infection that eliminated the single IgG immunoblot as sufficient laboratory evidence for surveillance purposes and thus reflects only recommended two-tier serologic test algorithms. Culture is extremely rare in practice and thus was not directly considered in this analysis. The proportion of confirmed cases that originated from clinicians and were not associated with positive laboratory evidence was indirectly estimated using the difference between the number of confirmed cases reported from a state in a given year and the number of individuals with confirmatory laboratory evidence in their system in that given year. Only some participating jurisdictions were able to verify the validity of this indirect calculation, and thus only figures from those states are provided. The overall ratio point estimate for each scenario reflects the mean of each ratio across observations per state and year. For scenario A, using existing laboratory evidence of infection, this calculation for each state and year was as follows:

$$\frac{\text{Number of individuals with laboratory evidence of infection}}{\text{Number of confirmed and probable cases reported to CDC}}$$

For scenario B, this calculation for each state and year was as follows:

$$\frac{\text{Number of individuals with two} - \text{tier serologic evidence}}{\text{Number of confirmed and probable cases reported to CDC}}$$

As this was a descriptive effort not based on sampling, statistical testing was not performed. This activity was reviewed by CDC and deemed a non-research activity not requiring further IRB review.

3 | RESULTS

During 2012–2018, an average of ~36,000 confirmed and probable Lyme disease cases were reported in the entire United States (range: ~31,000 [2012]–43,000 [2017]) (Centers for Disease Control & Prevention, 2016). On average, 24,854 confirmed cases and 9074 probable cases (average total = 33,928) were reported from 15 high-incidence states and reflected ~93%–96% of total cases reported in the US each year during 2012–2018. Among the 10 high-incidence states that provided data for this effort, a mean of ~2778 confirmed and probable cases were reported to CDC per state per year (range: 522–11,703 cases per state per year); 61 summary records per state and year were available for analysis.

A mean of 4864 individuals with laboratory evidence of infection were in surveillance systems of participating high-incidence states each year (range across states and years: 1302–20,994) (Table 1). On average, 35.5% of individuals with laboratory evidence of infection were ultimately classified as confirmed cases (range across states and years: 17.9%–57.9%), and 19.4% were ultimately classified as probable cases (range: 8.7%–34.7%; Table 1). In total, an average of 54.9% of individuals with laboratory evidence were formally reported to CDC as confirmed or probable cases of Lyme disease (range: 28.7%–85.8%). Nearly one-quarter (23.0%) of individuals with laboratory evidence of infection remained suspect cases because associated clinical information was not obtained (range: 2.1%–51.9%) and 17.7% were classified as not a case (range: 2.0%–36.9%; Table 1). Among the subset of total records for which clinical information was successfully obtained, the proportion deemed not a case was higher, with approximately one-quarter (26.4%) of individuals with laboratory evidence not meeting the clinical criteria to be classified as either confirmed or probable cases (range: 3.3%–44.3%).

Among 47 aggregate records per state per year for which serologic test type distribution was available, 248,158 individuals met surveillance criteria for laboratory evidence of infection: 120,240 (48.4%) individuals had positive two-tier IgM serologic testing, 104,247 (42.0%) had positive two-tier IgG testing; 69,316 (27.9%) of those individuals had both two-tier IgM and IgG evidence of infection. An additional 93,109 (37.5%) had only a single IgG immunoblot. The percent of records that ultimately became confirmed or probable cases did not substantially differ by test type (Table 2).

Among five states able to verify clinician-originated reports, an average of 17.9% (range: 7.6%–33.6%) of confirmed cases reported to CDC during 2012–2018 were not based on laboratory reports. Clinician-originated report of EM rash is the only circumstance in high-incidence states that does not require laboratory evidence of infection for surveillance case classification.

An average of 57% of laboratory reports and 53% of reported confirmed and probable cases were among males, with substantial variability in these proportions across states and years. Approximately 16% of individuals with laboratory evidence of infection were ≤14 years of age; an average of 18% of reported cases were from persons ≤14 years of age.

3.1 | Quantitative effect of two laboratory-based surveillance approaches on reported case counts

A laboratory-based surveillance approach based on current laboratory evidence of infection that includes two-tier serologic testing and single IgG immunoblots (scenario A) would yield 1.7 times (range across states and years: 1.3–2.7 times) the number of reported cases than reported on average from participating high-incidence states during 2012–2018. Under a surveillance approach using modified laboratory evidence of infection that eliminates the single IgG immunoblot and relies only on recommended two-tier serologic testing (scenario B), we estimate case counts from high-incidence states would average 1.2 times (range across states and years: 0.6–1.8 times) the number of cases reported from high-incidence states annually during 2012–2018.

4 | DISCUSSION

Over time, the large and increasing investigative burden of positive laboratory tests for Lyme disease in the most highly affected states has forced health departments to adjust in ways that interfere with the primary purpose of standardized surveillance and hinder interstate comparisons. Here, we utilized retrospective data collected during 2012–2018 in 10 states with an established high incidence of Lyme disease to better understand anticipated changes in case counts under a laboratory-based surveillance approach. In mid-2021, CSTE approved a modified surveillance case definition for Lyme disease that reflects a laboratory-based approach to surveillance for high-incidence states; it goes into effect in 2022 (Council of State & Territorial Epidemiologists, 2021). Laboratory evidence of infection was modified to remove single IgG immunoblot alone as laboratory evidence of infection for reports that would be provisioned to CDC, akin to scenario B assessed here. Consequently, we anticipate the number of reported cases per state under this new surveillance approach in high-incidence states to be on average 20% higher than those reported during 2012–2018. The first summary of cases by state under this new surveillance case definition will likely be made publicly available by CDC and individual states in late 2023.

Although a laboratory-based approach to Lyme disease surveillance in high-incidence states will substantially improve standardization across states and foster more meaningful use of public health resources, resulting case counts will be subject to specific biases, will not capture all incident cases and will include some previously cured infections. Counts will reflect bias towards disseminated stages of Lyme disease due to exclusion of direct clinician

reports of EM rash and low sensitivity of serologic testing in early Lyme disease (Branda et al., 2018; Steere, 2020). The frequency of various clinical manifestations in high-incidence states, including rare manifestations such as Lyme carditis, will not be captured through public health surveillance without active clinical follow-up; however, the true incidence of varied clinical manifestations was not previously measured reliably through public health surveillance due to its inherent biases (Mead, 2015). A modified two-tier serologic testing algorithm, in which the second-tier test is also an EIA, was first approved by the U.S. Food and Drug Administration (FDA) in 2019 (Mead et al., 2019) and was incorporated as laboratory evidence of infection in the new modified case definition. This testing approach provides improved sensitivity in early disease (Marques, 2018); its expansion into the diagnostic testing market could increase reported case counts in coming years by improving capture of early Lyme disease in a laboratory-based surveillance framework. Laboratory-based surveillance may also bias reported cases towards sociodemographic groups more likely to present for healthcare later in illness and away from those less likely to be subject to blood draws, such as children.

Under the new laboratory-based approach for high-incidence states, the sensitivity and specificity of Lyme disease case ascertainment will differ than under the previous case definitions. A net increase in sensitivity of case ascertainment is expected in most high-incidence states due to inclusion of individuals with laboratory evidence of infection who were not previously counted. Nearly one-quarter of total positive laboratory reports that were otherwise uninvestigated or unable to be classified (suspect cases) will be included, while <20% of confirmed cases from direct clinician reports and those that ended up classified as confirmed and probable cases based on single tier IgG immunoblot will not be included. The frequency of single IgG immunoblots varied greatly among states; in states where these made up a large proportion of the total positive laboratory reports, the number of reported cases under the revised definition could theoretically be lower than under the previous definition. In contrast, specificity will decline given the planned inclusion of the 18% of positive laboratory reports that were previously deemed ‘not a case’ after follow-up investigation. Depending on state criteria, the definition of ‘not a case’ could have included previously reported cases (e.g. reinfections) and laboratory positives that reflect prior infection not related to a current illness or false-positive findings. If the new case definition included single-tier positive IgG immunoblots among the laboratory criteria for cases in high-incidence states, the specificity would decrease further. Despite these variations in sensitivity and specificity, laboratory-based surveillance in high-incidences states will reflect a sustainable, standardized approach to monitoring trends and provide a baseline to evaluate changes across high-incidence states and over time.

Several factors preclude our ability to generate robust predictions of future reported Lyme disease case counts based on these retrospective data. First, there is inherent variability across jurisdictions in Lyme disease risk, surveillance practices, and system characteristics, exemplified by the wide range in the percent of individuals with laboratory evidence of infection that were classified as confirmed and probable Lyme disease cases, as well as the variability in the percent of individuals with positive laboratory evidence deemed not a case upon review of clinical information; such variability has been previously described within a single high-incidence state (Rutz et al., 2016). Also, the calculations presented

here assume static disease risk. However, there is demonstrable expansion of disease risk into new areas even in some states that already have a high incidence of Lyme disease. While these findings exemplify the need for improved standardization less reliant on human resource and interpretation, data presented here exclude those states that have made more major modifications to surveillance practices in recent years. As a result, the impact on total reported numbers that includes these other states remains unknown.

The surveillance case definition was substantively revised in 1996, 2007 and 2017 (Centers for Disease Control & Prevention, 2021a), but these modifications did not explicitly address the disparate public health objectives in high-incidence and low-incidence jurisdictions. In areas where human Lyme disease risk is already well established, human and entomologic surveillance data have demonstrated that risk can vary year to year but does not wane substantially (Burtis et al., 2016; Schwartz et al., 2017). Case counts do not generally elicit specific public health action or intervention that typically occurs with other reportable diseases (Cartter et al., 2018). In these areas, the goal of surveillance is to monitor trends, use case counts to raise clinician and public awareness to support prevention and early diagnosis and systematically measure effects of an intervention, such as a potential future second-generation Lyme disease vaccine. In contrast, in areas with emerging or previously absent disease risk, the goal of public health surveillance is to investigate cases thoroughly and with specificity, to determine the degree of local risk and to conduct outreach to promote prevention and early and accurate diagnosis and treatment.

Public health surveillance has generated valuable data on the epidemiology of Lyme disease since its inception in the early 1990s. However, a necessary paradigm shift is underway in how public health systems in high-incidence areas investigate and monitor trends in Lyme disease, a need clearly demonstrated by the COVID-19 pandemic. In 2020 and likely also in 2021, we anticipate a substantially decreased number of reported Lyme disease cases in the United States, a reality heavily influenced by artifact rather than variability in true disease incidence (McCormick et al., 2021). The pandemic placed strain on health department personnel that interfered with conduct of routine surveillance activities for other diseases, underscoring the need to increase utilization of more automated systems for disease tracking that are less subject to competing priorities of the public health workforce. Alternative data sources such as insurance claims repositories (Schwartz et al., 2021) and electronic medical records can complement changing surveillance practice and provide immense opportunities to analyse patterns associated with Lyme disease diagnoses, frequency of specific clinical manifestations, testing and treatment patterns and long-term outcomes to further the understanding of Lyme disease in a more detailed manner than currently possible through routine public health surveillance efforts.

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Impacts

- Public health follow-up to obtain clinical information on positive Lyme disease laboratory reports for surveillance case classification in high-incidence states is resource intensive; burden-reducing strategies have rendered surveillance non-standardized. Laboratory-based surveillance is a possible solution.
- Using data from 10 states with a high incidence of Lyme disease, we anticipate that a laboratory-based surveillance approach would, on average, yield 1.2 times the number of cases from high-incidence states than was reported by those states during 2012–2018.
- A laboratory-based surveillance approach for high-incidence states will improve standardization and reduce burden on public health systems, making more public health resources available for education and exploration of novel prevention strategies.

TABLE 1

Average number of individuals with positive laboratory evidence of infection according to final surveillance case classifications among 10 states with high incidence of Lyme disease, 2012–2018[a]

State[b]	Mean no. individuals with laboratory evidence of infection per year (range)	Percent of those with laboratory evidence that are confirmed (annual range of %)	Percent of those with laboratory evidence that are probable (annual range of %)	Percent of those with laboratory evidence that are 'not a case' upon investigation (range)	Percent of those with laboratory evidence that remain suspect (range)
1	8129 (6316–10,199)	34.0 (29.8–39.7)	12.0 (10.6–14.0)	19.5 (11.3–29.2)	34.7 (24.3–44.6)
2	2514(1650–3151)	28.8 (24.8–33.6)	15.5(12.3–18.5)	--	-
3	-	50.8 (40.2–57.9)	23.1 (14.2–29.1)	10.3 (5.9–15.0)	15.8 (4.3–30.7)
4	1430 (1302–1630)	32.8 (31.4–34.5)	28.3 (24.3–32.9)	7.8 (2.0–12.5)	30.8 (24.0–38.6)
5	5366 (4501–6259)	33.3(25.0–38.5)	28.5 (20.4–34.7)	3.9 (2.7–5.0)	34.2 (24.2–51.9)
6	2239 (1917–2610)	35.0 (29.3–41.0)	19.8 (17.5–25.2)	15.7(11.6–23.7)	29.5(26.6–36.2)
7	2103 (1318–2704)	-	-	-	-
8	13,676(7813–20,994)	39.3 (35.8–45.6)	11.5 (8.7–13.6)	30.8 (28.2–36.9)	18.4 (15.3–22.8)
9	2506(1930–3033)	41.9 (36.8–46.0)	28.0 (26.5–30.3)	26.3 (22.5–30.6)	3.8 (2.1–6.0)
10	4829 (4407–5229)	24.5 (17.9–31.2)	14.5 (10.8–19.1)	-	-
Mean	4864 (1302–20,994)	35.5 (17.9–57.9)	19.4 (8.7–34.7)	17.7(2.0–36.9)	23.0 (2.1–51.9)

[a]Laboratory evidence of infection and case classifications available here: https://ndc.services.cdc.gov/conditions/lyme-disease/. In brief, serologic positivity was either a two-tier IgM or IgG test, where the first tier was an enzyme immunoassay (EIA) or immunofluorescent assay (IFA), followed by a reflex immunoblot. Although not recommended to aid in patient diagnosis, a single IgG immunoblot was also sufficient laboratory evidence. A confirmed case of LD in already high-incidence areas was: (1) an erythema migrans (EM) rash documented by a healthcare provider; and (2) laboratory evidence of infection accompanied by at least one defined clinical manifestation. A probable case was any other case of clinician-diagnosed LD with laboratory evidence of infection. Suspect cases are those where clinical follow-up was attempted and unsuccessful or not attempted.

[b]States provided data that they felt were most representative of typical surveillance practice, and thus perhaps did not provide data for all variables or all years.

TABLE 2

Type of serological laboratory evidence of infection and percent of records classified as confirmed and probable cases among seven states with high incidence of Lyme disease, 2012–2018[a]

	Two-tier IgM		Two-tier IgG		Single-tier IgG	
State	**Percent confirmed (range)**	**Percent probable (range)**	**Percent confirmed (range)**	**Percent probable (range)**	**Percent confirmed (range)**	**Percent probable (range)**
1	37.8 (31.8-46.4)	12.9 (11.7-15.2)	36.6 (33.7-41.7)	12.5 (9.7-16.0)	30.4 (28.3-33.3)	10.0 (7.7-14.4)
2	27.7 (24.1-34.4)	15.1 (12.4-18.4)	37.0 (28.8-42.9)	18.2 (13.5-22.6)	31.6 (25.7-37.2)	15.5 (10.4-19.5)
4	38.8 (34.6-43.1)	26.4 (23.3-30.5)	34.9 (31.8-38.4)	29.8 (23.9-35.1)	22.6 (20.9-24.3)	27.2 (22.4-34.8)
5	34.4 (28.5-39.0)	23.1 (18.4-27.0)	32.7 (22.6-37.8)	32.3 (19.8-39.4)	34.5 (26.0-39.8)	30.7 (22.2-38.1)
6	41.0 (31.1-47.3)	18.9 (15.7-21.7)	41.0 (35.9-45.1)	21.3 (17.3-25.8)	29.4 (23.0-32.8)	19.7 (16.8-26.8)
8	45.2 (42.5-50.6)	27.6 (24.8-30.0)	45.0 (41.6-51.0)	31.8 (28.8-37.8)	35.9 (26.0-43.5)	31.2 (16.0-38.7)
9	38.8 (34.5-43.9)	11.5 (7.9-14.0)	38.9 (34.8-44.0)	11.6 (8.1-13.7)	40.1 (34.2-47.3)	11.4 (9.2-13.5)
Mean	37.7 (24.1–50.6)	18.6 (7.9–30.5)	38.5 (22.6–51.0)	21.5 (8.1–39.4)	32.3 (20.9–47.3)	19.7 (7.7–38.7)

[a]States 3,7,10 did not provide test breakdown information; serologic positivity was a two-tier IgM or IgG test, where the first tier was an enzyme immunoassay (EIA) or immunofluorescent assay (IFA), followed by a reflex immunoblot. Although not recommended to aid in patient diagnosis, a single IgG immunoblot was also sufficient laboratory evidence for surveillance purposes. A confirmed case of LD in already high-incidence areas was laboratory evidence of infection accompanied by at least one defined clinical manifestation. A probable case was any other case of clinician- diagnosed LD with laboratory evidence of infection. Two-tier data include persons positive for both IgM and IgG.