Modification of Lyme Disease Case Definition

This position statement updates the case definition for Lyme disease (previous 16-ID-10) to 1) define and standardize different approaches to public health surveillance for high-incidence and low-incidence jurisdictions in accordance with differing objectives; and 2) update laboratory evidence of infection.

I. Statement of the Problem

Lyme disease is a geographically focal tickborne disease, with >90% of cases being reported from 16 high incidence jurisdictions in the Northeast, mid-Atlantic, and Upper Midwest. While incidence has stabilized in these areas, incidence in surrounding states is increasing as is expansion in established populations of Ixodes scapularis ticks (1-3). The objectives of public health surveillance for Lyme disease in high-incidence jurisdictions and low-incidence jurisdictions are different. In high-incidence jurisdictions, information on cases is not used to guide an immediate public health response, but to describe the magnitude of the public health problem, monitor trends, and inform long-term community education and prevention efforts. In low-incidence and emerging jurisdictions, the objective is to identify specific geographic areas of risk to inform response efforts, clinical practice, and education of at-risk individuals.

At present, most high-incidence jurisdictions struggle to meet their public health objectives for Lyme disease. The current case definition requires that clinical information be obtained for classification of confirmed or probable cases. Given the immense volume of Lyme disease reports in high-incidence jurisdictions, investigation strains public health resources to an extent that may not be justified given the limited benefit of the data. In response, several high-incidence jurisdictions have adopted alternate surveillance approaches that reduce the human resource and fiscal burden. However, these approaches are not standardized and render modified case counts incongruent with the CSTE surveillance case definition and reporting criteria. Additionally, these practices prevent valid comparisons between jurisdictions.

A revision to the Lyme disease case definition is being proposed to 1) define and standardize approaches to public health surveillance for high-incidence and low-incidence jurisdictions in accordance with differing objectives; 2) increase specificity of the probable case classification in low-incidence states; 3) institute a tiered approach to laboratory evidence of infection; and 4) update laboratory evidence to reflect new developments.

II. Background and Justification

In the United States, Lyme disease is a tick-borne disease caused primarily by infection with Borrelia burgdorferi sensu stricto (4,5). Another related species, Borrelia mayonii, a pathogenic Borrelia burgdorferi sensu lato genospecies, has also been shown to cause Lyme disease in the upper midwestern United States (6,7). The majority of patients with Lyme disease present within 30 days of infection, typically with a characteristic rash (erythema migrans); untreated infection can involve multiple organ systems (5,8).

1) Historic surveillance data have shown that once populations of infected ticks are established in an area, the risk of Lyme disease does not wane (9,10). Hence, the objective of public health surveillance necessarily changes once risk is established, and surveillance in high incidence jurisdictions should also shift. This position statement proposes to modify the surveillance case definition to meet the needs of all jurisdictions by differentiating case classification criteria for jurisdictions based on incidence. This is
consistent with surveillance case definitions for nationally notifiable conditions that have different case classification criteria based on the mode of transmission (e.g., syphilis), acuity of the infection (e.g., Q fever), or location of transmission (indigenous vs imported, e.g., malaria). This position statement proposes to include laboratory reports for case classification absent clinical information in high-incidence jurisdictions, an approach that will increase the efficiency and comparability of Lyme disease surveillance in the most highly affected jurisdictions. Public health personnel from high-incidence states and CDC’s Lyme disease program performed a retrospective review of surveillance data in late 2019 to improve understanding regarding the quantitative considerations for a potential laboratory-only model. If this updated position statement is adopted, preliminary analysis suggests that the number of reported cases using a laboratory-only model is likely to be 1.2 times higher (range: 0.6-1.8) than what is currently reported to CDC from high-incidence states.

2) This position statement proposes to increase specificity within the probable case classification used by low-incidence states by removing “other physician diagnoses”.

3) Acknowledging the lack of specificity of the single-tier IgG immunoblot, a frequently reported test for Lyme disease, this position statement proposes to recategorize it as a category B (presumptive) test, given that it is not, by itself, recommended for laboratory diagnosis (11).

4) Finally, this position statement updates and expands laboratory criteria for evidence of infection by updating serologic testing criteria and adding PCR and direct detection of *B. burgdorferi* in tissue as acceptable laboratory evidence. A new modified two-tiered approach to serologic testing was approved by the United States Food and Drug Administration in 2019, allowing for an EIA rather than immunoblot as the second test in a Lyme disease testing algorithm (11, 12). While PCR lacks sensitivity for most Lyme disease diagnoses, it has proven useful in certain clinical circumstances (e.g., detecting evidence of the pathogen in synovial fluid and detecting *B. mayonii*) (7,13). Direct detection of *B. burgdorferi* spirochetes in biopsy and autopsy tissues has also been useful in establishing a diagnosis in Lyme disease-associated carditis deaths (14).

III. Statement of the desired action(s) to be taken

CSTE recommends the following actions:

1. Implement a standardized surveillance case definition for Lyme disease.
   A. Utilize standard sources (e.g. reporting*) for case ascertainment for Lyme disease. Surveillance for Lyme disease should use the recommended sources of data to the extent of coverage presented in Section V.
   B. Utilize standardized criteria for case ascertainment for Lyme disease presented in Section VI and Table VI in Technical Supplement.
   C. Utilize standardized criteria for case classification for Lyme disease presented in Section VII and Table VII in Technical Supplement.

2. Utilize standardized criteria for case ascertainment and classification (based on Sections VI and VII and Technical Supplement) for Lyme disease and **update** Lyme disease on the Nationally Notifiable Condition List

   - [ ] Immediately notifiable, extremely urgent (within 4 hours)
   - [ ] Immediately notifiable, urgent (within 24 hours)
   - [x] Routinely notifiable
   - [ ] No longer notifiable

3. CSTE recommends that all States and Territories enact laws (statute or rule/regulation as appropriate) to make this disease or condition reportable in their jurisdiction. Jurisdictions (e.g. States and Territories) conducting surveillance (according to these methods) should submit case notifications** to CDC.

4. Expectations for Message Mapping Guide (MMG) development for a newly notifiable condition: the National Notifiable Diseases Surveillance System (NNDSS) is transitioning to HL7-based messages for case notifications; the specifications for these messages are presented in MMGs.
When CSTE recommends a new condition be made nationally notifiable, CDC must obtain Office of Management and Budget Paperwork Reduction Act (OMB PRA) approval prior to accepting case notifications for the new condition. Under anticipated timelines, notification using the Generic V2 MMG would support transmission of the basic demographic and epidemiologic information common to all cases and could begin with the new MMWR year following the CSTE annual conference. Input from CDC programs and CSTE would prioritize development of a disease-specific MMG for the new condition among other conditions waiting for MMGs.

5. CDC should publish data on Lyme disease as appropriate (see Section IX). CSTE recommends the following case statuses be included in the CDC Print Criteria:
   - Confirmed
   - Probable
   - Suspect
   - Unknown

6. CSTE recommends that all jurisdictions (e.g. States, Localities, or Territories) with legal authority to conduct public health surveillance follow the recommended methods outlined in this recommendation and in the accompanying standardized surveillance position statement.

*Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance to local, state, or territorial public health.

**Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Conditions List to CDC.

IV. Goals of Surveillance

The objectives of public health surveillance for Lyme disease in high-incidence jurisdictions and low-incidence jurisdictions are different: in high-incidence jurisdictions, the objective is to monitor the burden and trends for Lyme disease in a population known to be at high risk of infection, while in low-incidence jurisdictions, the objective is to establish the risk of infection in a geographic area where risk has previously been poorly documented or absent in order to foster improved prevention and early diagnosis and treatment.

V. Methods for Surveillance: Surveillance for Lyme disease should use the recommended sources of data and the extent of coverage listed in Table V.

Laboratory reporting will be the most common source of data. A provisional review of data from 2012-2018 from several high incidence states (MA, NJ, MN, VA, VT, RI, MD, ME, PA) showed that laboratory reporting was by far the largest source of data and is the starting point for most case investigations. Electronically generated (or paper, when applicable) reports for positive tests should be reported, as well as post-mortem reports identifying suspected Borrelia spp, which may require additional manual medical records review. Laboratories should report all tests meeting the criteria listed in Section VI subsection A to public health authorities.

Additionally, healthcare providers and facilities who diagnose or become aware of Lyme disease cases should report them to public health authorities as required by state or local jurisdictions. Other data sources (e.g. hospital discharge data, diagnosis codes or death certificates) may be used as supplementary case finding methods.

<table>
<thead>
<tr>
<th>Table V. Recommended sources of data and extent of coverage for ascertainment of cases of Lyme disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source of data for case ascertainment</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Clinician reporting</td>
</tr>
<tr>
<td>Laboratory reporting</td>
</tr>
<tr>
<td>Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers), specify: hospitals</td>
</tr>
<tr>
<td>Death certificates</td>
</tr>
<tr>
<td>Hospital discharge or outpatient records</td>
</tr>
</tbody>
</table>
Extracts from electronic medical records | X
---|---
Telephone survey |  
School-based survey |  
Other, specify: N/A |  

VI. Criteria for case ascertainment

A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

Lyme disease surveillance should be routine, ongoing, and reported to public health authorities using standard case reporting timeframes.

A1. Clinical Criteria for Reporting
- Erythema migrans rash

A2. Laboratory Criteria for Reporting
- Isolation of *B. burgdorferi* or *B. mayonii* in culture, OR
- Detection of *B. burgdorferi* or *B. mayonii* in a clinical specimen by a *B. burgdorferi* group-specific NAAT assay, OR
- Detection of *B. burgdorferi* group-specific antigens by immunohistochemical assay on biopsy or autopsy tissues, OR
- Antibody to *B. burgdorferi* detected by EIA or IFA, OR
- An immunoblot test positive for *B. burgdorferi*-specific IgM or IgG

A3. Epidemiologic Linkage Criteria for Reporting
None

A4. Vital Records Criteria for Reporting
- A death certificate listing Lyme disease as a cause of death or a significant condition contributing to death.

A5. Other Criteria for Reporting
- Any person whose healthcare record contains a diagnosis of Lyme disease, OR
- Findings on autopsy consistent with *Borrelia* spp. infection, e.g., in cardiac tissue.

B. Disease-specific data elements to be included in the initial report
N/A

VII. Case Definition for Case Classification

A. Narrative: Description of criteria to determine how a case should be classified.

A1. Clinical Criteria¹

An illness characterized by one of the following early or late-stage manifestations, as reported by a healthcare provider, and in the absence of another known etiology:

- Erythema migrans (EM) rash. For purposes of surveillance, EM is defined as a skin lesion (observed by a healthcare provider) that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach a size of ≥5 cm in diameter.

*Note: Secondary lesions also may occur.*

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¹ Refer to Appendix A for additional information when evaluating clinical criteria.
• **Musculoskeletal system.** Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints.

*Note: Objective joint swelling may sometimes be followed by chronic arthritis in one or a few joints.*

• **Nervous system.** Any of the following signs that cannot be explained by any other etiology, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (unilateral or bilateral); radiculoneuropathy; or, rarely, encephalomyelitis.

• **Cardiovascular system.** Acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks.

*Note: Atrioventricular conduction defects may sometimes be associated with myocarditis.*

### A2. Laboratory Criteria

For the purposes of surveillance, laboratory evidence includes:

#### Confirmatory laboratory evidence:

1. Isolation of *B. burgdorferi* sensu stricto or *B. mayonii* in culture, OR
2. Detection of *B. burgdorferi* sensu stricto or *B. mayonii* in a clinical specimen by a *B. burgdorferi* group-specific NAAT assay, OR
3. Detection of *B. burgdorferi* group-specific antigens by immunohistochemical assay on biopsy or autopsy tissues, OR
4. Positive serologic tests\(^2\) in a two-tier or equivalent format, including:
   a. Standard two-tier test (STTT): a positive or equivocal first-tier screening assay, often an enzyme immunoassay [EIA] or immunofluorescence assay [IFA] for IgM, IgG, or a combination of immunoglobulins, followed by a concordant positive IgM\(^3\) or IgG\(^4\) immunoblot interpreted according to established criteria, OR
   b. Modified two-tier test (MTTT): positive or equivocal first-tier screen, followed by a different, sequential positive or equivocal EIA in lieu of an immunoblot as a second-tier test\(^5\).

#### Presumptive laboratory evidence:

1. Positive IgG immunoblot\(^6\), interpreted according to established criteria\(^4\), without positive or equivocal first-tier screening assay

*Note: The categorical labels used here to stratify laboratory evidence are intended to support the standardization of case classifications for public health surveillance. The categorical labels should not be used to interpret the utility or validity of any laboratory test methodology.*

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\(^2\) Currently, there are no serologic tests available for *B. mayonii* infection, but cross-reactivity with *B. burgdorferi* testing may occur.

\(^3\) IgM WB is considered positive when at least two of the following three bands are present: 24 kDa (OspC)*, 39 kDa (BmpA), and 41 kDa (Fla). Low incidence states should disregard IgM results for specimens collected >30 days after symptom onset. *Depending upon the assay, OspC could be indicated by a band of 21, 22, 23, 24 or 25 kDa.

\(^4\) IgG WB is considered positive when at least five of the following 10 bands are present: 18 kDa, 24 kDa (OspC)*, 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa. *Depending upon the assay, OspC could be indicated by a band of 21, 22, 23, 24 or 25 kDa.

\(^5\) The MTTT algorithm should be performed using assays specifically cleared by the US Food and Drug Administration (FDA) for this purpose. (Mead et al, 2019)

\(^6\) While a single IgG WB is adequate for surveillance purposes, a two-tier test is still recommended for clinical diagnosis.
A3. Epidemiologic Linkage
None

A4. Case Classifications

High-incidence jurisdictions are those that have had an average Lyme disease incidence of ≥10 confirmed cases/100,000 population for a period of three consecutive years. At the time of this statement (spring 2021), those jurisdictions are: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, Wisconsin, and the District of Columbia (http://www.cdc.gov/lyme/stats/tables.html).

Low-incidence jurisdictions are those that have not had an average Lyme disease incidence of ≥10 confirmed cases/100,000 population for a period of three consecutive years. Once ≥10 confirmed cases/100,000 population have been observed in a low-incidence jurisdiction for a period of three consecutive years, they become a high-incidence jurisdiction for the purposes of surveillance and should permanently switch reporting criteria.

For determining incidence for case classification and reporting purposes, calculations should be made at the state or territory level. Case classification for reporting should not be differentially applied at the subdivision level.

A clinically compatible case is defined as a case that meets the clinical criteria defined above.

High-incidence jurisdictions (as defined above)

Confirmed: N/A

Probable: A case that meets confirmatory laboratory evidence.

Suspect: A case that meets presumptive laboratory evidence.

Low-incidence jurisdictions (as defined above)

Confirmed: A clinically compatible case that meets confirmatory laboratory criteria.

Probable: A clinically compatible case that meets presumptive laboratory criteria.

Suspect:
- A case that meets confirmatory or presumptive laboratory criteria, but no clinical information is available, OR
- A case of erythema migrans rash with no laboratory evidence of infection.

Note: This CSTE case definition is intended solely for public health surveillance purposes and does not recommend diagnostic criteria for clinical partners to utilize in diagnosing patients with potential Lyme Disease.

B. Criteria to distinguish a new case of this disease or condition from reports or notifications which should not be enumerated as a new case for surveillance

A new case is one that has not been reported within the same calendar year (January through December).7

VIII. Period of Surveillance

Surveillance should be ongoing.

7 Using calendar year allows case counting which more closely corresponds with the seasonality of Lyme disease than using a number of months between case reports.
IX. Data sharing/release and print criteria

CSTE recommends the following case statuses* be included in the ‘case’ count released outside of the public health agency:

- Confirmed
- Probable
- Suspect
- Unknown

* Which case statuses are included in the case counts constitute the “print criteria.”

Jurisdictions (e.g., States and Territories) conducting surveillance under this case definition can voluntarily submit de-identified case information to CDC, if requested and in a mutually agreed upon format.

Additional Guidance:
- Finalized state-specific aggregate data are published annually via CDC WONDER. Summary data are also made available through the CDC Lyme disease website. Longer articles describing trends are published on an ad-hoc basis.
- CDC may re-release finalized data on ad hoc basis for research or public health activities in accordance with the Data Release Guidelines for the National Notifiable Diseases Surveillance System.

X. Revision History

<table>
<thead>
<tr>
<th>Position Statement ID</th>
<th>Section of Document</th>
<th>Revision Description</th>
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<tr>
<td>16-ID-10</td>
<td>Updated case definition</td>
<td>Modified exposure criteria to improve specificity of reported cases in low-incidence jurisdictions</td>
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<td>16-ID-10</td>
<td>I. Statement of the Problem</td>
<td>Updated to:</td>
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<td>- Provide revised statement of the problem</td>
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<td>- Meet revised template requirements</td>
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<td>16-ID-10</td>
<td>II. Background and Justification</td>
<td>Updated to:</td>
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<td>- Provide up-to-date data and information</td>
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<td>- Summarize case definition updates</td>
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<td>16-ID-10</td>
<td>III. Desired Actions to be Taken</td>
<td>Updated to meet revised template requirements</td>
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<td>16-ID-10</td>
<td>IV. Goals of Surveillance</td>
<td>Specified goals of surveillance for high- vs. low-incidence jurisdictions</td>
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<tr>
<td>16-ID-10</td>
<td>V. Methods for Surveillance</td>
<td>Updated to include narrative text per revised template requirements.</td>
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<td>VI. Criteria for Case Ascertainment</td>
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<td>16-ID-10</td>
<td>VII. Case Definition for Case Classification – Clinical Criteria</td>
<td>Clinical Criteria: minor grammatical changes made</td>
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<td>16-ID-10</td>
<td>VII. Case Definition for Case Classification – Laboratory Criteria</td>
<td>Updated to include:</td>
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<td>- Removed CSF Antibody testing</td>
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<tr>
<td></td>
<td></td>
<td>- Minor grammatical changes made</td>
</tr>
<tr>
<td>16-ID-10</td>
<td>VII. Case Definition for Case Classification – Epidemiologic Linkage</td>
<td>Updated to clarify exposures in high- vs. low-incidence jurisdictions</td>
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<tr>
<td>16-ID-10</td>
<td>VII. Case Definition for Case Classification – Case Classifications</td>
<td>Updated to include classifications for high- vs. low-incidence jurisdictions</td>
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<td>XI. References</td>
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<tr>
<td>10-ID-06</td>
<td>Transfer to new position statement format</td>
<td>Added tables needed for electronic disease reporting.</td>
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<td>07-ID-11</td>
<td>Updated case definition</td>
<td>Updated laboratory testing criteria and added endemcity definition</td>
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<td>1990</td>
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</table>
XI. Cited References


XII. Coordination

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Technical Supplement

Table VI. Table of criteria to determine whether a case should be reported to public health authorities.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Reporting Lyme disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Erythema migrans rash</td>
<td>S</td>
</tr>
<tr>
<td><strong>Laboratory Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>B. burgdorferi</em> or <em>B. mayonii</em> in culture</td>
<td>S</td>
</tr>
<tr>
<td>Detection of <em>B. burgdorferi</em> or <em>B. mayonii</em> in a clinical specimen by a <em>B. burgdorferi</em> group-specific NAAT assay</td>
<td>S</td>
</tr>
<tr>
<td>Detection of <em>B. burgdorferi</em> group-specific antigens by immunohistochemical assay on biopsy or autopsy tissues</td>
<td>S</td>
</tr>
<tr>
<td>Antibody to <em>B. burgdorferi</em> detected by EIA or IFA</td>
<td>S</td>
</tr>
<tr>
<td>An immunoblot test positive for <em>B. burgdorferi</em>-specific IgM or IgG</td>
<td>S</td>
</tr>
<tr>
<td><strong>Vital Records Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>A death certificate listing Lyme disease as a cause of death or a significant condition contributing to death</td>
<td>S</td>
</tr>
<tr>
<td><strong>Other Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Any person whose healthcare record contains a diagnosis of Lyme disease</td>
<td>S</td>
</tr>
<tr>
<td>Findings on autopsy consistent with <em>Borrelia</em> spp. infection</td>
<td>S</td>
</tr>
</tbody>
</table>

Notes:
S = This criterion alone is SUFFICIENT to report a case.
Table VII. Classification Table: Criteria for defining a case of Lyme disease.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>High Incidence States</th>
<th>Low Incidence States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suspect</td>
<td>Probable</td>
</tr>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td></td>
<td></td>
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<tr>
<td>Erythema migrans rash</td>
<td>N</td>
<td>O</td>
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<tr>
<td>Objective joint swelling</td>
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<tr>
<td>Lymphocytic meningitis</td>
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<td>Cranial neuritis</td>
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<tr>
<td>Encephalomyelitis</td>
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<tr>
<td>High-grade atrioventricular conduction defects (2nd-degree or 3rd-degree)</td>
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<tr>
<td>No clinical information available</td>
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<tr>
<td>Clinical symptoms reported by healthcare provider</td>
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<tr>
<td>Absence of another known etiology</td>
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<tr>
<td><strong>Laboratory Evidence</strong></td>
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<tr>
<td>Isolation of <em>B. burgdorferi</em> sensu stricto or <em>B. mayonii</em> in culture</td>
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</tr>
<tr>
<td>Detection of <em>B. burgdorferi</em> sensu stricto or <em>B. mayonii</em> in a clinical specimen by a <em>B. burgdorferi</em> group-specific NAAT assay</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>Detection of <em>B. burgdorferi</em> group-specific antigens by immunohistochemical assay on biopsy or autopsy tissues</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>Standard Two-Tier Test (STTT)²</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Positive or equivocal result for serum antibody to <em>B. burgdorferi</em> by EIA or IFA</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Positive immunoblot for <em>B. burgdorferi</em>-specific IgM³ or IgG⁴</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Modified Two-Tier test (MTTT)²,⁵</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Positive or equivocal result for serum antibody to <em>B. burgdorferi</em> by EIA or IFA</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Positive or equivocal result for serum antibody to <em>B. burgdorferi</em> by different, sequential EIA</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Positive IgG immunoblot⁶ (in the absence of a positive or equivocal first-tier screening assay)</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>No laboratory evidence of infection</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Criteria to distinguish a new case:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported within the same calendar year (January through December)</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Notes:
- S = This criterion alone is SUFFICIENT to classify a case.
- N = All “N” criteria in the same column are NECESSARY to classify a case. A number following an “N” indicates that this criterion is only required for a specific disease/condition subtype (see below). If the absence of a criterion (i.e., criterion NOT present) is required for the case to meet the classification criteria, list the absence of criterion as a necessary component.
- O = At least one of these “O” (ONE OR MORE) criteria in each category (categories = clinical evidence, laboratory evidence, and epidemiologic evidence) in the same column—is required to classify a case. A number following an “O” indicates that this criterion is only required for a specific disease/condition subtype.
- ²Currently, there are no serologic tests available for *B. mayonii* infection, but cross-reactivity with *B. burgdorferi* testing may occur.
- ³IgM WB is considered positive when at least two of the following three bands are present: 24 kDa (OspC)*, 39 kDa (BmpA), and 41 kDa (Fla). Low incidence states should disregard IgM results for specimens collected >30 days after symptom onset. *Depending upon the assay, OspC could be indicated by a band of 21, 22, 23, 24 or 25 kDa.
- ⁴IgG WB is considered positive when at least five of the following 10 bands are present: 18 kDa, 24 kDa (OspC)*, 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa. *Depending upon the assay, OspC could be indicated by a band of 21, 22, 23, 24 or 25 kDa.
- ⁵The MTTT algorithm should be performed using assays specifically cleared by the US Food and Drug Administration (FDA) for this purpose. (Mead et al, 2019)
- ⁶While a single IgG WB is adequate for surveillance purposes, a two-tier test is still recommended for clinical diagnosis.
Appendix A: Guidance for Implementation of Clinical Criteria

Symptoms need to be reported by a healthcare provider. Patient-reported symptoms do not meet clinical criteria.

An illness characterized by one of the following early or late-stage manifestations, as reported by a healthcare provider:

- **Erythema migrans (EM) rash.** For purposes of surveillance, EM is defined as a skin lesion (observed by a healthcare provider) that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach a size of ≥5 cm in diameter. Secondary lesions also may occur. Annular erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM. For most patients, the expanding EM lesion is accompanied by other acute symptoms, particularly fatigue, fever, headache, mildly stiff neck, arthralgia, or myalgia. These symptoms are typically intermittent.

- **Musculoskeletal system.** Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints. Manifestations not considered as criteria for case classification include chronic progressive arthritis not preceded by brief attacks and chronic symmetrical polyarthritis. Additionally, arthralgia, myalgia, or fibromyalgia syndromes alone are not criteria for musculoskeletal involvement.

- **Nervous system.** Any of the following signs that cannot be explained by any other etiology, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (unilateral or bilateral); radiculoneuropathy; or, rarely, encephalomyelitis. Headache, fatigue, paresthesia, or mildly stiff neck alone are not criteria for neurologic involvement.

- **Cardiovascular system.** Acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis. Palpitations, bradycardia, bundle branch block, or myocarditis alone are not criteria for cardiovascular involvement.