Committee: Infectious Disease

Title: Changes to Public Health Reporting and National Notification for Spotted Fever Rickettsiosis (including Rocky Mountain Spotted Fever)

Synopsis:
This position statement updates the case definition for Spotted Fever Rickettsiosis (SFR) (including Rocky Mountain spotted fever [RMSF]) (previous position statement 09-ID-16) through changes to the laboratory criteria.

I. Statement of the Problem

CSTE position statement 09-ID-16 developed a standardized reporting definition for SFR (including RMSF) to facilitate timely, complete, and standardized local and national reporting. However, the limitations with current serologic assays and the recognition of multiple spotted fever group Rickettsiae (SFGR) contribute to potential inaccurate interpretation of diagnostic test results and raise concerns regarding the accuracy of current surveillance data (Moncayo et al., 2010; Kakumanu et al., 2018).

The current case definition incorporates results of a positive immunoglobulin M (IgM) serologic assay and a single positive immunoglobulin G (IgG) serologic assay, as laboratory evidence for probable cases. Yet, neither is reliable in definitively diagnosing acute illness. An IgM antibody response has been shown to be inaccurate in identifying acute illness and therefore insufficient to diagnose SFR (McQuiston et al., 2014). In addition, data suggest that the prevalence of IgG antibodies reactive to SFGR in asymptomatic individuals may be more common than previously assumed. The presence of these IgG antibodies may reflect past exposures rather than acute cases thereby confounding the interpretation of a single IgG antibody test result (Marshall et al., 2003).

Due to these limitations, we propose updating the current laboratory criteria used to classify SFR. Many states have already adopted modified case definitions within their jurisdiction (e.g., raising the cut-off titer used to investigate lab reports) to help focus investigations towards suspect patients more likely to be cases.

We also propose that final SFR case numbers be included in NNDSS annual tables and omitted from the weekly NNDSS tables. SFR cases are complex to classify and reporting of reliable case numbers is often delayed, making weekly case numbers of limited utility. Some case numbers in the weekly NNDSS tables are deleted after case review so these numbers may not reflect SFR trends and are inconsistent with final data.

II. Background and Justification

SFR are a group of diseases caused by closely related SFGR. These pathogens cause acute febrile illnesses, with headache, malaise, thrombocytopenia, rash, and occasionally eschars (dark necrotic scab at the site of tick or mite bite). RMSF, caused by R. rickettsii, is well recognized as the most severe rickettsial illness (Biggs et al., 2016; Drexler et al., 2016; Raoult & Paddock, 2005).

RMSF has been nationally notifiable since the 1920s. In 2010, RMSF became reportable under the category of SFR, which captures cases of RMSF, *Rickettsia parkeri* rickettsiosis, Pacific Coast tick fever, and others. In the early stages of disease, it can be difficult to clinically distinguish between RMSF and other SFR (Delisle et al., 2016). Commercially available serologic tests are unable to differentiate between these SFGR species (Gage & Jerrells, 1992). There is increasing suspicion that other SFGR may be responsible for many of the SFR cases, including diseases associated with *R. parkeri*, *R. amblyommatis*, *R. montanensis*, *R. massiliae* *R. rhipicephali*, and *Rickettsia* species 364D (Dahlgren et al., 2016; Paddock, 2005; Sonenshine, 2018).

Currently, only 3% of SFR cases are reported as confirmed, and most of our understanding of SFR is based on incomplete and often uninterpretable diagnostic evidence, including single serologic titers and/or qualitative antibody results. Antibodies to SFGR can rise in the first week of illness and elevation can persist for months or years following infection. Differentiation of persistent and incident antibodies requires the use of quantitative indirect immunofluorescence antibody assays (IFA) on paired samples, taken 2–4 weeks apart. However, laboratory testing for the majority of SFR cases falls short of this standard, resulting in a skewed understanding of SFR epidemiology and national disease burden (Hilton et al., 1999; Marshall et al., 2003; Vaughn et al., 2014). In addition, data suggest that the prevalence of IgG antibodies reactive to SFGR in asymptomatic individuals may be more common than previously assumed and confounds the interpretation of single IgG antibody test results, which may reflect past exposures rather than incident cases (Marshall et al., 2003).

Diagnostic methods, such as IFA to detect IgM, enzyme-linked immunosorbent assay (ELISA), and latex agglutination, currently accepted as supportive laboratory evidence, are non-specific serologic tests with significant limitations that may cloud our understanding of SFR burden (Crump et al., 2004; Kato et al., 2013; McQuiston et al., 2014). Closely related species of SFGR have cross-reactive antigens and cannot be definitely distinguished using commonly available serologic assays.

SFR incidence varies in the United States and many jurisdictions receive an excessive number of SFGR positive serologic assays with very low titers. Many jurisdictions have implemented their own case definition to reduce the burden of investigations, which leads to challenges in national surveillance. Surveillance that is standardized across state jurisdictions is necessary to successfully monitor the geographic and temporal occurrence of these diseases and maintain awareness in clinicians and public health officials.

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

CSTE recommends the following actions:

1. Implement a standardized surveillance case definition for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever).
   
   A. Utilize standard sources (e.g. reporting*) for case ascertainment for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever). Surveillance for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) should use the recommended sources of data to the extent of coverage presented in Section V.
   
   B. Utilize standardized criteria for case ascertainment for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) presented in Section VI and Table VI in Technical Supplement.

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2 https://www.cdc.gov/nndss/infectious-tables.html
c. Utilize standardized criteria for case classification for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) presented in Sections 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 Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) and retain Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) on the Nationally Notifiable Condition List.

☐ Immediately notifiable, extremely urgent (within 4 hours)
☐ Immediately notifiable, urgent (within 24 hours)
☒ 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 Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) as appropriate (see Section IX for additional information).

** NNC data sharing/release and print criteria

CSTE recommends the following case statuses be included in the CDC Print Criteria:
☒ Confirmed
☒ Probable
☐ Suspect
☐ Unknown

We propose that final SFR case numbers be included in the NNDSS annual tables and omitted from the weekly NNDSS tables. SFR cases are complex to classify and reporting of reliable case numbers is often delayed, making weekly case numbers of limited utility when comparing week to week or to that week in previous years. Some case numbers reported in the weekly NNDSS tables are deleted after case review so these numbers may not accurately reflect SFR trends and are inconsistent with final data.

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.
IV. Goals of Surveillance

The improved case definition will update the interpretation of laboratory results and their translation into surveillance data, with an emphasis on excluding interpretations that may not reflect current SFGR infections in patients. Surveillance will continue to provide information on the temporal, geographic, and demographic occurrence of SFR (including RMSF) to facilitate its prevention and control.

V. Methods for Surveillance: Surveillance for Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) should use the recommended sources of data and the extent of coverage listed in Table V.

The majority of SFR cases are identified through laboratory and healthcare provider reporting. A provisional review of reported case data from AZ, NC and NYC from 2015 through 2018 reveals that 81–97% of all reported cases are identified through electronic laboratory reporting. Additional cases may also be ascertained from supplemental data sources including physician reports, death certificates, hospital discharge or outpatient records, and electronic medical records.

Table V. Recommended sources of data and extent of coverage for ascertainment of cases of Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever).

<table>
<thead>
<tr>
<th>Source of data for case ascertainment</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population-wide</td>
</tr>
<tr>
<td>Clinician reporting</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory reporting</td>
<td>X</td>
</tr>
<tr>
<td>Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers), specify:</td>
<td>X</td>
</tr>
<tr>
<td>Death certificates</td>
<td>X</td>
</tr>
<tr>
<td>Hospital discharge or outpatient records</td>
<td>X</td>
</tr>
<tr>
<td>Data from electronic medical records</td>
<td>X</td>
</tr>
<tr>
<td>Telephone survey</td>
<td></td>
</tr>
<tr>
<td>School-based survey</td>
<td></td>
</tr>
<tr>
<td>Other, specify:</td>
<td></td>
</tr>
</tbody>
</table>

VI. Criteria for case ascertainment

A positive laboratory diagnostic result for SFR triggers a laboratory report to public health officials, which would then conduct a disease investigation to determine whether the individual meets the clinical presentation criteria for case ascertainment. Healthcare providers also report known or suspected cases of SFR to the health department, which would also trigger a disease investigation. SFR cases may also be identified through supplemental data sources including death certificates listing SFR (including RMSF) as a cause of death or significant condition contributing to death, or medical records containing a diagnosis of SFR.
A. Narrative: A description of suggested criteria for case ascertainment of a specific condition.

A1. Clinical Criteria for Reporting
N/A

A2. Laboratory Criteria for Reporting
Report any illness to public health authorities that meets any of the following laboratory criteria:

Any patient with laboratory evidence of SFR (including RMSF) including any of the following:

- Detection of SFGR nucleic acid in a clinical specimen via amplification of a *Rickettsia* genus- or species-specific target by polymerase chain reaction (PCR) assays, OR
- Elevated IgG antibody titer in one or more serology samples reactive with SFGR antigen by IFA, OR
- Demonstration of SFGR antigen in a biopsy or autopsy specimen by IHC, OR
- Isolation of SFGR from a clinical specimen in cell culture and molecular confirmation (e.g., PCR or sequence).

A3. Epidemiologic Linkage Criteria for Reporting
None required

A4. Vital Records Criteria for Reporting
Report any illness to public health authorities that meets any of the following vital records criteria:
A person whose death certificate lists SFR (including RMSF) as a cause of death or a significant condition contributing to death.

A5. Other Criteria for Reporting
Report any illness of person whose healthcare record contains a diagnosis of Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever).

B. Disease-specific data elements to be included in the initial report
None.

VII. Case Definition for Case Classification

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

A1. Clinical Criteria
Fever as reported by the patient or a healthcare provider, AND one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or any hepatic transaminase elevation.

A2. Laboratory Criteria

*Confirmatory laboratory evidence:*

- Detection of SFGR nucleic acid in a clinical specimen via amplification of a *Rickettsia* genus- or species-specific target by PCR assay, OR
- Serological evidence of a fourfold increase in IgG-specific antibody titer reactive with SFGR antigen by IFA between paired serum specimens (one taken in the first two
weeks after illness onset and a second taken two to ten weeks after acute specimen collection)*, OR
- Demonstration of SFGR antigen in a biopsy or autopsy specimen by IHC, OR
- Isolation of SFGR from a clinical specimen in cell culture and molecular confirmation (e.g., PCR or sequence).

*Presumptive laboratory evidence:
- Has serologic evidence of elevated IgG antibody at a titer ≥1:128 reactive with SFGR antigen by IFA in a sample taken within 60 days of illness onset.**

*Supportive laboratory evidence:
- Has serologic evidence of elevated IgG antibody at a titer <1:128 reactive with SFGR antigen by IFA in a sample taken within 60 days of illness onset.

*A four-fold rise in titer should not be excluded (as confirmatory laboratory criteria) if the acute and convalescent specimens are collected within two weeks of one another.
**This includes paired serum specimens without evidence of fourfold rise in titer, but with at least one single titer ≥1:128 in IgG-specific antibody titers reactive with SFGR antigen by IFA.

A3. Epidemiologic Linkage

None required for case classification.

A4. Case Classifications

*Confirmed:
- A clinically compatible case (meets clinical criteria) that is laboratory confirmed.

*Probable:
- A clinically compatible case (meets clinical criteria) that has presumptive laboratory evidence.

*Suspect:
- A case with confirmatory or presumptive laboratory evidence of infection with no clinical information available, OR
- A clinically compatible case (meets clinical criteria) that has supportive laboratory evidence.

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 person previously reported as a probable or confirmed case-patient may be counted as a new case-patient when there is an episode of new clinically compatible illness with confirmatory laboratory evidence.

VIII. Period of Surveillance

Surveillance should be ongoing.
IX. Data sharing/release and print criteria

1. 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.”

2. 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.

   Production of national data summaries and national data re-release for non-NNCs:
   - Prior to release of national data summaries CDC should follow the CDC/ATSDR Policy on Releasing & Sharing Data, issued on April 16, 2003 and referenced in 11-SI-01 and custodians of such data should consult the CDC-CSTE Intergovernmental Data Release Guidelines Working Group report (www.cste2.org/webpdfs/drgwgreport.pdf) which contains data release guidelines and procedures for CDC programs re-releasing state, local, or territorial-provided data.
   - CDC programs have a responsibility, in collaboration with states, localities, and territories, to ensure that CDC program-specific data re-release procedures meet the needs of those responsible for protecting data in the states and territories.

Additional Guidance:
- Notification to CDC of probable and confirmed cases of SFR is recommended.
- Finalized data are published in the annual NNDSS tables. Summaries and analyses of reported cases of SFR, including RMSF, are compiled and published periodically dependent upon accumulation of data and changes in disease activity and regional incidence.
- State-specific compiled data will continue to be published in the annual NNDSS tables.
- No specific plans for re-release. However, CDC may re-release finalized data on ad hoc basis for research of 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>
</tr>
</thead>
<tbody>
<tr>
<td>09-ID-16</td>
<td>I and II</td>
<td>Discuss the non-specificity of certain diagnostic methods. Discuss the burden of case investigations leading to jurisdictions implementing own case definitions. Recommend that SFR surveillance data be included in the annual NNDSS tables and omitted from weekly NNDSS tables.</td>
</tr>
<tr>
<td>09-ID-16</td>
<td>III.</td>
<td>Add the utilization of standard sources, standardized criteria for case ascertainment, and standardized criteria for case classification information. Recommend that SFR surveillance data be included in the annual NNDSS tables and omitted from weekly NNDSS tables.</td>
</tr>
<tr>
<td>09-ID-16</td>
<td>IV.</td>
<td>Update the goals of surveillance to include the information about the interpretation of laboratory results and their translation into surveillance data, with an emphasis on excluding interpretations that may not reflect current SFGR infections in patients.</td>
</tr>
<tr>
<td>09-ID-16</td>
<td>V.</td>
<td>Add statement about how the majority of cases are identified though laboratory and healthcare reporting.</td>
</tr>
<tr>
<td>09-ID-16</td>
<td>VI. A2</td>
<td>Moved PCR detection to the top of laboratory reporting criteria to emphasize the availability of the Rickettsia species Real Time-PCR Assay available through the Laboratory Response Network (LRN). Require the diagnostic serum specimen to be collected within 60 days of illness onset. Remove elevated IgG antibody reactive with <em>R. rickettsii</em> or other SFG by ELISA, dot-ELISA, or latex agglutination as lab criteria. Remove elevated IgM antibody reactive with <em>R. rickettsii</em> or other SFG by IFA, ELISA, dot-ELISA, or latex agglutination as lab criteria. Added a vital records criteria for reporting.</td>
</tr>
</tbody>
</table>
| 09-ID-16 | VII. A1., A2., A3., A4., and B. | A1. Clarify “fever as reported by the patient or a healthcare provider” as part of the clinical criteria. A2. Require acute serum specimen to be collected within first two weeks of illness onset date. A2. Require a convalescent serum specimen with a fourfold rise in IgG titer collected up to 10 weeks later as confirmatory laboratory evidence. A2. Add an elevated IgG IFA antibody titer to be at least 1:128 in value in a serum specimen collected within 60 days of illness onset as presumptive laboratory evidence. A2. Added asterisks indicating presumptive laboratory evidence also includes paired serum specimens without evidence of fourfold rise in titer, but with at least one single titer ≥1:128 in IgG-specific antibody titers reactive with SRGR antigen by IFA. A2. Remove elevated IgG antibody reactive with *R. rickettsii* or other SFG by ELISA, dot-ELISA, or latex agglutination as laboratory supportive criteria. A2. Remove elevated IgM antibody reactive with *R. rickettsii* or other SFG by IFA, ELISA, dot-ELISA, or latex agglutination as laboratory supportive criteria. A2. Add elevated IgG IFA antibody titer of <1:128 in a sample taken within 60 days of illness onset as supportive laboratory evidence. A3. Remove sentence regarding epidemiologic evidence/linkage/exposure and changed it to "none required". A4. Update the suspect case classification to have two categories: 
  • A case with laboratory evidence of infection but either no clinical information available, OR |
<table>
<thead>
<tr>
<th>09-ID-16</th>
<th>IX. Update the language regarding when finalized data are published.</th>
</tr>
</thead>
</table>

**XI. References**


### XII. Coordination

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

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Detection of spotted fever group <em>Rickettsia</em> nucleic acid in a clinical specimen via amplification of a Rickettsia genus or species-specific target by PCR assays</td>
<td>S</td>
</tr>
<tr>
<td>Elevated IgG antibody titer reactive with spotted fever group <em>Rickettsia</em> antigen by IFA</td>
<td>S</td>
</tr>
<tr>
<td>Demonstration of spotted fever group <em>Rickettsia</em> antigen in a biopsy or autopsy specimen by IHC</td>
<td>S</td>
</tr>
<tr>
<td>Isolation of spotted fever group <em>Rickettsia</em> from a clinical specimen in cell culture and molecular confirmation (e.g., PCR or sequence).</td>
<td>S</td>
</tr>
<tr>
<td><strong>Vital Records Criteria for Reporting</strong></td>
<td></td>
</tr>
<tr>
<td>A person whose death certificate lists Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever) 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>A person whose healthcare record contains a diagnosis of Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever).</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 Spotted Fever Rickettsiosis (including Rocky Mountain spotted fever).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Suspect</th>
<th>Probable</th>
<th>Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever as reported by the patient or a healthcare provider</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Rash</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Eschar</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Headache</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Myalgia</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Anemia</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Any hepatic transaminase elevation</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>No clinical information is available</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Evidence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection of spotted fever group <em>Rickettsia</em> nucleic acid in a clinical specimen via amplification of a <em>Rickettsia</em> genus or species-specific target by PCR assays</td>
<td>O</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Four-fold increase in IgG specific antibody titer reactive with spotted fever group <em>Rickettsia</em> antigen by indirect immunofluorescence assay (IFA) between paired serum specimens (one taken in the first two weeks of illness onset and a second taken two to ten weeks after acute specimen collection). A fourfold rise in titer should not be excluded (as confirmatory laboratory criteria) if the acute and convalescent specimens are collected within two weeks of one another.</td>
<td>O</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Demonstration of spotted fever group <em>Rickettsia</em> antigen in a biopsy or autopsy specimen by IHC</td>
<td>O</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Isolation of spotted fever group <em>Rickettsia</em> from a clinical specimen in cell culture and molecular confirmation (e.g., PCR or sequence).</td>
<td>O</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Elevated IgG antibody titer (≥1:128 in at least one serology sample taken within 60 days of illness onset) reactive with spotted fever group <em>Rickettsia</em> antigen by IFA</td>
<td>O</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Elevated IgG antibody at a titer &lt;1:128 reactive with spotted fever group <em>Rickettsia</em> antigen by IFA in a sample taken within 60 days of illness onset.</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Criteria to distinguish a new case:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case not previously reported to public health authorities should be classified as a new case.</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>A clinically compatible case should be counted as new when laboratory results were reported beyond 60 days of date of illness onset.</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Notes:
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—in conjunction with all “N” criteria 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.