09-ID-15

Committee: Infectious

Title: Public Health Reporting and National Notification for Ehrlichiosis and Anaplasmosis

I. Statement of the Problem

CSTE position statement 07-EC-02 recognized the need to develop an official list of nationally notifiable conditions and a standardized reporting definition for each condition on the official list. The position statement also specified that each definition had to comply with American Health Information Community recommended standards to support "automated case reporting from electronic health records or other clinical care information systems." In July 2008, CSTE identified sixty-eight conditions warranting inclusion on the official list, each of which now requires a standardized reporting definition.

II. Background and Justification

Background[1]

Human ehrlichioses and anaplamosis are tick-borne diseases cause by a number of similar organisms. Ehrlichiosis is caused by *Ehrlichia chaffeensis* and less commonly, *Ehrlichia ewingii*. Anaplasmosis is caused by *Anaplasma phagocytophilum*. Cases have been reported from most states, with the majority of ehrlichiosis cases coming from south-central and the southeastern United States and most anaplasmosis cases being reported from the north-east and upper mid-West. Over 500 cases of ehrlichiosis and over 500 cases of anaplasmosis are reported each year in the United States, but the there is evidence that the diagnosis may not be made in many more cases. Ongoing surveillance is needed to establish the burden of disease and better define the epidemiology of the various infections caused by *Ehrlichia* and *Anaplasma* species. This information will be used to better inform medical professionals about the disease and tailor prevention messages for the public.

Justification

Ehrlichiosis and Anaplasmosis meets the following criteria for a nationally and **standard** notifiable condition, as specified in CSTE position statement 08-EC-02:

- A majority of state and territorial jurisdictions—or jurisdictions comprising a majority of the US population—have laws or regulations requiring **standard** reporting of ehrlichiosis and anaplasmosis to public health authorities
- CDC requests **standard** notification of ehrlichiosis and anaplasmosis to federal authorities
- CDC has condition-specific policies and practices concerning the agency's response to, and use of, notifications.

[1] Much of the material in the background is directly quoted from the CDC's ehrlichiosis and anaplasmosis websites. See the references for further information on this source.

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

CSTE requests that CDC adopt this standardized reporting and classification definition for ehrlichiosis and anaplasmosis to facilitate timelier, complete, and standardized local and national reporting of this condition.

IV. Goals of Surveillance

To provide information on the temporal, geographic, and demographic occurrence of ehrlichiosis and anaplasmosis to facilitate its prevention and control.

V. Methods for Surveillance

Surveillance for ehrlichiosis and anaplasmosis should use the sources of data and the extent of coverage listed in Table V.

Table V. Recommended sources of data and extent of coverage for ascertaining cases of ehrlichiosis and anaplasmosis.

	Coverage	
Source of data for case ascertainment	Population-wide	Sentinel sites
clinician reporting	X	
laboratory reporting	X	
reporting by other entities (e.g., hospitals, veterinarians, pharmacies)	X	
death certificates	X	
hospital discharge or outpatient records	X	
extracts from electronic medical records	X	
telephone survey		
school-based survey		
other _____		

VI. Criteria for Reporting

Reporting refers to the process of healthcare providers or institutions (e.g., clinicians, clinical laboratories, hospitals) submitting basic information to governmental public health agencies about cases of illness that meet certain reporting requirements or criteria. Cases of illness may also be ascertained by the secondary analysis of administrative health data or clinical data. The

purpose of this section is to provide those criteria that should be used by humans and machines to determine whether a specific illness should be reported.[2]

A. Narrative description of criteria to be used by humans to determine whether a case should be reported to public health authorities

Report any illness to public health authorities that meets any of the following criteria:

1. Any person with clinical and laboratory evidence of infection with *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, *Anaplasma phagocytophilum*, or Ehrlichiosis/anaplasmosis undetermined species.
Ehrlichia ewingii or Anaplasma phagocytophilum. Laboratory evidence of infection includes any of the following:

a. A fourfold change in *E. chaffeensis* or *A. phagocytophilum* -specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples
b. Elevated IgG antibody reactive with *E. chaffeensis* or *A. phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays
c. Elevated IgM antibody reactive with *E. chaffeensis* or *A. phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays
d. Detection of *E. chaffeensis, E. ewingii,* or *A. phagocytophilum* -specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)
e. Demonstration of *E. chaffeensis* or *A. phagocytophilum* –specific antigen in a biopsy or autopsy sample by immunohistochemical methods
f. Isolation of *E. chaffeensis* or *A. phagocytophilum* from a clinical specimen in cell culture
g. Identification of morulae in monocytes, granulocytes, or macrophages by microscopic examination

2. A person whose healthcare record contains a diagnosis of ehrlichiosis or anaplasmosis.

3. A person whose death certificate lists ehrlichiosis or anaplasmosis as a cause of death or a significant condition contributing to death.

Other recommended reporting procedures

- All cases of ehrlichiosis and anaplasmosis should be reported.
- Reporting should be on-going and routine.

[2] "Human-based" criteria (described below under "A. Narrative") can be applied by medical care providers and laboratory staff based on clinical judgment and clinical diagnosis. Machine-based criteria (described below under "B. Table") can be applied using computerized algorithms that operate in electronic health record systems, including computerized records of laboratory test orders and laboratory test results; other clinical data systems (e.g., hospital discharge data systems serving multiple hospitals); or administrative data (e.g., healthcare provider billing data, vital records, and EMS data).

- Frequency of reporting should follow the state health department's routine schedule.

B. Table of criteria to be used by machines to determine whether a case should be reported to public health authorities

Table VI-B. Proposed Table of criteria to determine whether a case should be reported to public health authorities. Note: The following criteria are proposed for evaluation before general implementation. For purposes of currently implementing reporting the narrative description in VI-A, should be used.

Criterion	Reporting	
Clinical Presentation		
Fever	C	
Headache	C	
Myalgias	C	
Anemia	C	
Leukopenia	C	
Thrombocytopenia	C	
Elevated Hepatic Transaminases	C	
Nausea	C	
Vomiting	C	
Rash	C	
Healthcare record contains a diagnosis of Ehrlichiosis or Anaplasmosis		S
Death certificate lists Ehrlichiosis or Anaplasmosis as a cause of death or a significant condition contributing to death		S
Laboratory findings		
A fourfold change in *Ehrlichia chaffeensis* specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O	
Detection of *Ehrlichia chaffeensis*-specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O	
Demonstration of *Ehrlichia chaffeensis* antigen in a biopsy or autopsy sample by immunohistochemical methods	O	
Isolation of *Ehrlichia chaffeensis* from a clinical specimen in cell culture	O	
Elevated IgG antibody to *Ehrlichia chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-	O	

ELISA, or other assays		
Elevated IgM antibody to *Ehrlichia chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays	O	
Detection of *Ehrlichia ewingii*-specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O	
A fourfold change in *Anaplasma phagocytophilum*-specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O	
Detection of *Anaplasma phagocytophilum*-specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O	
Demonstration of *Anaplasma phagocytophilum* antigen in a biopsy or autopsy sample by immunohistochemical methods	O	
Isolation of *Anaplasma phagocytophilum* from a clinical specimen in cell culture	O	
Elevated IgG antibody to *Anaplasma phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays	O	
Elevated IgM antibody *Anaplasma phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays	O	
Identification of morulae in monocytes, granulocytes, or macrophages	O	
Epidemiological risk factors		
History of having been in potential tick habitat in the 14 days prior to the onset of illness	C	
History of a tick bite	C	

Notes:
S = This criterion alone is sufficient to report a case
O = At least one of these "O" criteria in each category in the same column (e.g., clinical presentation and laboratory findings) is required to report a case.
C = This finding corroborates (i.e., supports) the diagnosis of—or is associated with—Ehrlichiosis, but is not included in the case definition and is not required for reporting.
A requisition or order for any of the "S" laboratory tests is sufficient to meet the reporting criteria. A requisition or order for any of the "O" laboratory tests—in conjunction with at least one of any "O" criteria in the other non-laboratory categories in the same column—is sufficient to meet the reporting criteria.

C. Disease Specific Data Elements:

Disease-specific data elements to be included in the initial report are listed below.
(To be added)

VII. Case Definition for Case Classification

A. Narrative description of criteria to determine whether a case should be classified as confirmed, probable (presumptive), or suspected (possible).

Clinical presentation

A tick-borne illness characterized by acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases. Nausea, vomiting, or rash may be present in some cases.

Clinical evidence

Any reported fever and one or more of the following: headache, myalgia, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation.

Epidemiologic evidence

A history of having been in a tick habitat in the 14 days before illness onset; history of a tick bite is not required. List occupation if relevant to exposure. Travel in the past 14 days; location of travel.

Laboratory evidence

For the purposes of surveillance,

1. ***Ehrlichia chaffeensis* infection** (formerly included in the category Human Monocytic Ehrlichiosis [HME]):

   Laboratory confirmed:
   - Serological evidence of a fourfold change in immunoglobulin G (IgG)-specific antibody titer to *E. chaffeensis* antigen by indirect immunofluorescence assay (IFA) between paired serum samples (one taken in first week of illness and a second 2-4 weeks later), **or**
   - Detection of *E. chaffeensis* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **or**
   - Demonstration of ehrlichial antigen in a biopsy or autopsy sample by immunohistochemical methods, **or**
   - Isolation of *E. chaffeensis* from a clinical specimen in cell culture.

Laboratory supportive:

- Serological evidence of elevated IgG or IgM antibody reactive with *E. chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of ≥1:64 and does not use IgM test results independently as diagnostic support criteria.), **or**
- Identification of morulae in the cytoplasm of monocytes or macrophages by microscopic examination.

2. ***Ehrlichia ewingii*** infection (formerly included in the category Ehrlichiosis [unspecified, or other agent]):

   Laboratory confirmed:
   - Because the organism has never been cultured, antigens are not available. Thus, *Ehrlichia ewingii* infections may only be diagnosed by molecular detection methods: *E. ewingii* DNA detected in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay.

3. ***Anaplasma phagocytophilum* infection** (formerly included in the category Human Granulocytic Ehrlichiosis [HGE]):

   Laboratory confirmed:
   - Serological evidence of a fourfold change in IgG-specific antibody titer to *A. phagocytophilum* antigen by indirect immunofluorescence assay (IFA) in paired serum samples (one taken in first week of illness and a second 2-4 weeks later), **or**
   - Detection of *A. phagocytophilum* DNA in a clinical specimen via amplification of a specific target by polymerase chain reaction (PCR) assay, **or**
   - Demonstration of anaplasmal antigen in a biopsy/autopsy sample by immunohistochemical methods, **or**
   - Isolation of *A. phagocytophilum* from a clinical specimen in cell culture.

   Laboratory supportive:

   - Serological evidence of elevated IgG or IgM antibody reactive with A. phagocytophilum antigen by IFA, enzyme-linked immunosorbent Assay (ELISA), dot-ELISA, or assays in other formats (CDC uses an IFA IgG cutoff of ≥1:64 and does not use IgM test results independently as diagnostic support criteria.), **or**
   - Identification of morulae in the cytoplasm of neutrophils or eosinophils by microscopic examination.

4. **Human ehrlichiosis/anaplasmosis – undetermined:**
   - See below

Exposure

Exposure is defined as having been in potential tick habitats within the past 14 days before onset of symptoms. A history of a tick bite is not required.

Case Classification

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

Probable: A clinically compatible case (meets clinical evidence criteria) that has supportive laboratory results. For ehrlichiosis/anaplasmosis – an undetermined case can only be classified as probable. This occurs when a case has compatible clinical criteria with laboratory evidence to support ehrlichia/anaplasma infection, but not with sufficient clarity to definitively place it in one of the categories previously described. This may include the identification of morulae in white cells by microscopic examination in the absence of other supportive laboratory results.

Suspect: A case with laboratory evidence of past or present infection but no clinical information available (e.g. a laboratory report).

Comment

There are at least three species of bacteria, all intracellular, responsible for ehrlichiosis/ anaplasmosis in the United States: *Ehrlichia chaffeensis*, found primarily in monocytes, and *Anaplasma phagocytophilum* and *Ehrlichia ewingii*, found primarily in granulocytes. The clinical signs of disease that result from infection with these agents are similar, and the range distributions of the agents overlap, so testing for one or more species may be indicated. Serologic cross-reactions may occur among tests for these etiologic agents.

Four sub-categories of confirmed or probable ehrlichiosis/anaplasmosis should be reported: 1) human ehrlichiosis caused by *Ehrlichia chaffeensis*, 2) human ehrlichiosis caused by *E. ewingii*, 3) human anaplasmosis caused by *Anaplasma phagocytophilum*, or 4) human ehrlichiosis/anaplasmosis - undetermined. Cases reported in the fourth sub-category can only be reported as "probable" because the cases are only weakly supported by ambiguous laboratory test results.

Problem cases for which sera demonstrate elevated antibody IFA responses to more than a single infectious agent are usually resolvable by comparing the levels of the antibody responses, the greater antibody response generally being that directed at the actual agent involved. Tests of additional sera and further evaluation via the use of PCR, IHC, and isolation via cell culture may be needed for further clarification. Cases involving persons infected with more than a single etiologic agent, while possible, are extremely rare and every effort should be undertaken to resolve cases that appear as such (equivalent IFA antibody titers) via other explanations.

Current commercially available ELISA tests are not quantitative, cannot be used to evaluate changes in antibody titer, and hence are not useful for serological confirmation. Furthermore,

IgM tests are not always specific and the IgM response may be persistent. Therefore, IgM tests are not strongly supported for use in serodiagnosis of acute disease.

B. Classification Tables

Table VII-B lists the criteria that must be met for a case to be classified as confirmed, probable (presumptive), or suspected (possible).

Table VII-B. Proposed table of criteria to determine whether a case is classified. Note: The following criteria are proposed for evaluation before general implementation. For purposes of current notification, the narrative description in VII-A, should be used.

	Case Definition		
Criterion	Confirmed	Probable	Suspected
Clinical Presentation			
Fever	N	N	
Headache	O	O	
Myalgias	O	O	
Anemia	O	O	
Leukopenia	O	O	
Thrombocytopenia	O	O	
Elevated Hepatic Transaminases	O	O	
Nausea	C	C	
Vomiting	C	C	
Rash	C	C	
Laboratory findings			
A fourfold change in *Ehrlichia chaffeensis* specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O1		O1
Detection of *Ehrlichia chaffeensis* - specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O1		O1
Demonstration of *Ehrlichia chaffeensis* antigen in a biopsy or autopsy sample by immunohistochemical methods	O1		O1
Isolation of *Ehrlichia chaffeensis* from a clinical specimen in cell culture	O1		O1
Elevated IgG antibody to *Ehrlichia*		O1	O1

chaffeensis antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays			
Elevated IgM antibody to *Ehrlichia chaffeensis* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O1	O1
Detection of *Ehrlichia ewingii* -specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	N2		O2
A fourfold change in *Anaplasma phagocytophilum* -specific immunoglobulin G (IgG) antibody titer by indirect immunofluorescence assay (IFA) between paired serum samples	O3		O3
Detection of *Anaplasma phagocytophilum* -specific nucleic acid in a clinical specimen by polymerase chain reaction (PCR)	O3		O3
Demonstration of *Anaplasma phagocytophilum* antigen in a biopsy or autopsy sample by immunohistochemical methods	O3		O3
Isolation of *Anaplasma phagocytophilum* from a clinical specimen in cell culture	O3		O3
Elevated IgG antibody to *Anaplasma phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O3	O3
Elevated IgM antibody *Anaplasma phagocytophilum* antigen by IFA, enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or other assays		O3	O3
Identification of morulae in monocytes, granulocytes, or macrophages	C1,C2,C3	C1,C2,C3,N4	O4
Epidemiological risk factors			
History of having been in potential tick habitat in the 14 days prior to the onset of illness	C	C	
History of a tick bite	C	C	

Notes:

N = This criterion in conjunction with all other "N" and any "O" criteria in the same column is required to classify a case. A number following an "N" indicates that this criterion is only required for a specific clinical presentation
O = At least one of these "O" criteria in each category in the same column (e.g., clinical presentation and laboratory findings)—in conjunction with all other "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 clinical presentation.
C = This finding corroborates (i.e., supports) the diagnosis of—or is associated with—Ehrlichiosis, but is not included in the case definition and is not required for classification. A number following a "C" indicates that this criterion is compatible with a specific clinical presentation.
1 = *Ehrlichia chaffeensis* infection
2 = *Ehrlichia ewingii* infection
3 = *Anaplasma phagocytophilum* infection
4 = Human ehrlichiosis/anaplasmosis – undetermined

VIII. Period of Surveillance

Surveillance should be on-going.

IX. Data sharing/release and print criteria

- Notification to CDC of probable and confirmed cases for Ehrlichiosis and Anaplasmosis is recommended.

- Summaries and analyses of reported cases of ehrlichiosis/anaplasmosis are compiled and published periodically dependent upon accumulation of data and changes in disease activity and regional incidence. A summary and analyses of national surveillance and epidemiology of ehrlichiosis and anaplasmosis in the U.S. was published in 2005. A manuscript covering diagnosis and management of rickettsial diseases including ehrlichioses and anaplasmosis in the U.S. was published in 2006.

- Annual state case totals and national incidence rates are available via MMWR.

- Final verification of case counts with SHDs is usually completed by August of the year following the surveillance year and reported annually in the National Summary of Notifiable Diseases - United States published in March or April of the subsequent year.

- Aggregate numbers of cases the United States are available to WHO via MMWR.

X. References

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XI. Coordination:

Agencies for Response:

(1) Thomas R. Frieden, MD, MPH
Director
Centers for Disease Control and Prevention
1600 Clifton Road, NE
Atlanta GA 30333

(404) 639-7000
txf2@cdc.gov

XII. Submitting Author:

(1) Jeffrey Engel
State Health Director
North Carolina Department of Health
1931 Mail Service Center
Raleigh, NC 27699-1931
Jeffrey.engel@ncmail.net

Co-Authors:

(1) Associate Member
Harry F. Hull, Medical Epidemiologist
HF Hull & Associates, LLC
1140 St. Dennis Court
Saint Paul, MN 55116
(651) 695-8114
hullhf@msn.com

(2) Associate Member
Cecil Lynch, Medical Informaticist
OntoReason
7292 Shady Woods Circle
Midvale, UT 84047
(916) 412.5504
clynch@ontoreason.com

(3) Associate Member
R. Gibson Parrish, Medical Epidemiologist
P.O. Box 197
480 Bayley Hazen Road
Peacham, VT 05862
(802) 592-3357
gib.parrish@gmail.com