16-ID-02

Committee: Infectious Disease

Title: Standardized Surveillance Case Definition for Histoplasmosis

I. Statement of the Problem

Histoplasmosis, caused by the fungus *Histoplasma capsulatum*, encompasses a spectrum of disease ranging from self-limited respiratory illness to disseminated infection. *H. capsulatum* is an environmental fungus found worldwide that replicates well in nitrogen-rich soil, such as soil enriched by bird and bat droppings. In the United States, histoplasmosis is caused primarily by *Histoplasma capsulatum var. capsulatum* and is endemic in the Ohio and Mississippi River valleys as well as other areas. Another variety of *H. capsulatum* (*var. duboisii*, sometimes referred to as *H. duboisii*), causes a disease known as African histoplasmosis, which has rarely been reported in the United States. There is no standardized case definition for histoplasmosis in the United States, limiting our understanding of its epidemiology and how and why outbreaks occur. This position statement proposes a standardized case definition for histoplasmosis.

II. Background and Justification

Histoplasmosis is one of the most common endemic mycosis in the United States, yet the true number of cases is unknown and is difficult to ascertain without a standardized case definition (*1-2*). Based on hospital discharge data, >5,000 histoplasmosis-associated hospitalizations were estimated to have occurred in 2012; however, the total number of annual histoplasmosis cases is likely much higher because most persons with this infection do not require hospitalization (*3*).

Histoplasmosis is typically acquired through inhalation of spores found in soil contaminated with bird or bat droppings. No direct human-to-human transmission has been reported. Symptoms generally develop 3–14 days after exposure, although many infections are asymptomatic (*4-6*). Acute pulmonary histoplasmosis is the most common form of disease, and symptoms typically include fever, headache, malaise, and cough. Severe pulmonary disease can involve a wide range of complications (*4*). Disseminated disease can also occur, usually in immunocompromised patients (*4)*. Most cases of histoplasmosis are self-limited, but patients with persistent symptoms or moderate or severe disease require treatment with antifungals (*6*).

Several laboratory methods are available for diagnosis of histoplasmosis, including culture, histopathology, and antigen, antibody, and nucleic acid testing. Culture remains the gold standard but requires weeks to grow, and cultures are often negative in mild to moderate pulmonary infection (*6-7*). Histopathology is another method for detecting *H. capsulatum* yeast in sputum, blood, or tissue samples; however, other fungi can appear morphologically similar, such as *Blastomyces dermatitidis*, *Candida glabrata*, *Cryptococcus* and *Coccidioides* spp. (*7*). Antibody testing for histoplasmosis by complement fixation (CF) and immunodiffusion (ID) is also available. Paired serum samples showing seroconversion (≥4-fold rise in CF titer or detection of M band by ID assay after documented negative on previous test) and detection of H band by ID assay provide greatest specificity, but a single serum or cerebrospinal fluid CF titer ≥1:32 or M band can also aid in diagnosis (*6*). Production of antibodies may not occur in immunocompromised patients (*7*). *H. capsulatum* antigen testing of serum, urine, or other body fluid by enzyme immunoassay is also available and is highly sensitive in disseminated disease but less so in acute pulmonary disease (*6*). *B. dermatitidis* infections can result in false-positive antigen tests for *H. capsulatum*. Detection of *H. capsulatum* DNA in clinical specimens by validated nucleic acid tests, such as polymerase chain reaction (PCR), can also be used in diagnosis.

Histoplasmosis is not a nationally notifiable disease, and a standard case definition has not been established. The ten states and one territory (Arkansas, Delaware, Illinois, Indiana, Kentucky, Michigan, Minnesota, Nebraska, Pennsylvania, Wisconsin and Puerto Rico) in which the disease is reportable each have different case definitions (*8*). Although most of the case definitions include broadly similar clinical and

laboratory criteria, the differences that exist limit data comparability. Additionally, the jurisdictions collect different laboratory, clinical, and epidemiological data elements. Most require laboratories or healthcare personnel to report a case of histoplasmosis within a certain timeframe to the local or state health department electronically through the state's surveillance system or by mailing or faxing a completed disease case report.

To address the substantial variability in how states conduct surveillance on histoplasmosis, a workgroup was formed to develop a consensus case definition. Participants in this workgroup represented state health departments from ten states (Arkansas, Illinois, Indiana, Kentucky, Michigan, Mississippi, Nebraska, Ohio, Tennessee, and Wisconsin), CDC's Mycotic Diseases Branch, and the academic community. A consensus surveillance definition for histoplasmosis would allow for the comparison of incidence of histoplasmosis cases between states and aid in the investigation of disease trends.

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

1. Utilize standard sources (e.g. reporting*) for case ascertainment for histoplasmosis. Surveillance for histoplasmosis should use the following recommended sources of data to the extent of coverage presented in Table III.

Table III. Recommended sources of data and extent of coverage for ascertainment of cases of histoplasmosis.

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	X	
Laboratory reporting	X	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers)	X	
Death certificates	X	
Hospital discharge or outpatient records	X	
Extracts from electronic medical records	X	
Telephone survey		
School-based survey		
Other _____		

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2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for histoplasmosis but do not add histoplasmosis to the *Nationally Notifiable Condition List*. If requested by CDC, jurisdictions (e.g. States and Territories) conducting surveillance according to these methods may submit case information to CDC.

CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined above.

Terminology:
* Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local or state public health.
**Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Condition List TO CDC.

IV. Goals of Surveillance

To provide information on the temporal, geographic, and demographic occurrence of both outbreak-associated and sporadic histoplasmosis cases in the United States.

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

The primary source of data will be from laboratory reporting. In states where histoplasmosis is a reportable condition, laboratories should report histoplasmosis cases to public health authorities. Healthcare facilities and clinicians who become aware of patients with histoplasmosis should also report these to public health authorities. Other data sources (e.g., death certificates or hospital discharge data) may be used as supplementary case finding methods.

VI. Criteria for case identification

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

In public health jurisdictions where histoplasmosis is classified as a reportable disease or condition, clinicians and laboratories should report to public health authorities any of the following laboratory results:

- Culture of *H. capsulatum* from a clinical specimen,
- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by histopathology,
- ≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers taken at least 2 weeks apart,
- Detection in serum of H band by *H. capsulatum* immunodiffusion antibody test,
- Detection in serum of M band by *H. capsulatum* immunodiffusion antibody test after a documented lack of M band on a previous test (i.e., seroconversion),
- Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., PCR),
- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by cytopathology,
- Detection in serum or cerebrospinal fluid (CSF) of *H. capsulatum* antibodies by single complement fixation titer of 1:32 or greater (e.g., 1:64),
- Detection in serum or cerebrospinal fluid (CSF) of M band by *H. capsulatum* immunodiffusion antibody test without a previous negative test,
- Detection of *H. capsulatum* antigen in serum, urine, or other body fluid by an enzyme immunoassay test.

Report to public health authorities any patient who is suspected to have histoplasmosis based on clinical suspicion and is epidemiologically linked to a confirmed case.

Report to public health authorities a person whose healthcare record contains a diagnosis of histoplasmosis or a person whose death certificate lists histoplasmosis a cause of death or significant condition contributing to death.

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

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

Criterion	Histoplasmosis Reporting	
Clinical Evidence		
Clinical suspicion of histoplasmosis	N	
Health record diagnosis of histoplasmosis		S
Death certificate lists histoplasmosis as cause of death or significant condition contributing to death		S
Laboratory Evidence		
Culture of *H. capsulatum* from a clinical specimen		S
Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by histopathology		S

≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers taken at least 2 weeks apart		S
Detection in serum of H band by *H. capsulatum* immunodiffusion antibody test		S
Detection in serum of M band by *H. capsulatum* immunodiffusion antibody test after a documented lack of M band on a previous test (i.e., seroconversion)		S
Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., PCR).		S
Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by cytopathology		S
Detection in serum or cerebrospinal fluid (CSF) of *H. capsulatum* antibodies by single complement fixation titer of 1:32 or greater (e.g., 1:64)		S
Detection in serum or cerebrospinal fluid (CSF) of M band by *H. capsulatum* immunodiffusion antibody test without a previous negative test		S
Detection of *H. capsulatum* antigen in serum, urine, or other body fluid by an enzyme immunoassay test		S
Epidemiological Evidence		
Epidemiologically linked to a confirmed case	N	
		2016 Template

Notes:
S = This criterion alone is Sufficient to report a case.
N = All "N" criteria in the same column are Necessary to report a case.
O = At least one of these "O" (One or more) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to report a case.
* A requisition or order for any of the "S" laboratory tests is sufficient to meet the reporting criteria.

C. Disease-specific data elements

Clinical Information:

- Description of clinical symptoms and signs of illness
- Date of onset
- Hospitalization
- Underlying diseases/co-infections

Laboratory Information:

- Date of collection of first specimen that indicated histoplasmosis
- Specimens indicative of histoplasmosis:
    - Specimen type
    - Specimen collection date
    - Laboratory test performed
    - Results, including *H. capsulatum* variety (i.e., var. *capsulatum* or var. *duboisii*), if known

Epidemiological Information:

- Environmental exposure likely to contribute risk of illness
- Occupation
- Travel history from past 2 years
    - Outside of state of residence
    - Outside of the United States

VII. Case Definition for Case Classification

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

Clinical Criteria
Clinical presentation includes either:

- At least two of the following clinical findings:
  - fever,
  - chest pain,
  - cough,
  - myalgia,
  - shortness of breath,
  - headache, or
  - erythema nodosum/erythema multiforme rash; **OR**

- At least one of the following clinical findings:
  - Abnormal chest imaging (e.g., pulmonary infiltrates, cavitation, enlarged hilar or mediastinal lymph nodes, pleural effusion);
  - Clinical evidence of disseminated disease:
    - gastrointestinal ulcerations or masses;
    - skin or mucosal lesions;
    - peripheral lymphadenopathy;
    - pancytopenia, as evidence of bone marrow involvement;
    - enlargement of the liver, spleen, or abdominal lymph nodes; or
    - meningitis, encephalitis, or focal brain lesion.

Laboratory Criteria
Confirmatory laboratory criteria:

- Culture of *H. capsulatum* from a clinical specimen,
- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by histopathology,
- ≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers taken at least 2 weeks apart,
- Detection in serum of H band by *H. capsulatum* immunodiffusion antibody test,
- Detection in serum of M band by *H. capsulatum* immunodiffusion antibody test after a documented lack of M band on a previous test (i.e., seroconversion),
- Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., PCR).

Non-confirmatory laboratory criteria:

- Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by cytopathology,
- Detection in serum or cerebrospinal fluid (CSF) of *H. capsulatum* antibodies by single complement fixation titer of 1:32 or greater (e.g., 1:64),
- Detection in serum or cerebrospinal fluid (CSF) of M band by *H. capsulatum* immunodiffusion antibody test without a previous negative test,
- Detection of *H. capsulatum* antigen in serum, urine, or other body fluid by an enzyme immunoassay test.

Epidemiologic Linkage
Epidemiologically linked (e.g.: common environmental exposure) with a confirmed case.

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

Probable Case:
A clinically-compatible case that meets non-confirmatory laboratory criteria*; **OR**

A case that meets confirmatory laboratory criteria, but no clinical information is available; **OR**

A clinically-compatible case that does not meet laboratory criteria, but is epidemiologically linked to a confirmed case.

*Illness in a person with compelling evidence (e.g., culture, histopathology, seroconversion) of a different fungal infection, such as blastomycosis or coccidioidomycosis, and meeting only non-confirmatory laboratory criteria for histoplasmosis should not be counted as a case of histoplasmosis since other fungal infections can cause false positive *H. capsulatum* antigen and antibody test results.

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

Following acute histoplasmosis, complement fixation titers and M-band on immunodiffusion antibody testing typically remain elevated for several years. People with chronic histoplasmosis may have cultures yielding *H. capsulatum* and positive antigen enzyme immunoassay testing for months or more. Distinct repeat infections have also been reported, typically involving acute pulmonary disease in endemic areas.

To minimize duplicate counting of chronic infections and missed repeat acute infections, illnesses in a given person should be counted no more than once every 24 months.

B. Classification Tables

Table VII-B. Criteria for defining a case of histoplasmosis.

Criterion	Confirmed		Probable				
Clinical Evidence							
At least two of the following: fever, chest pain, cough, myalgia, shortness of breath, headache, or erythema nodosum/erythema multiforme rash	N		N			N	
Abnormal chest imaging		O		O			O
Clinical evidence of disseminated disease		O		O			O
Laboratory Evidence							
Culture of *H. capsulatum* from a clinical specimen	O	O			O		
Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by histopathology	O	O			O		
≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers taken at least 2 weeks apart	O	O			O		
Detection in serum of H band by *H. capsulatum* immunodiffusion antibody test	O	O			O		
Detection in serum of M band by *H. capsulatum* immunodiffusion antibody test after a documented lack of M band on a previous test (i.e., seroconversion)	O	O			O		
Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., PCR).	O	O			O		
Identification of characteristic *H. capsulatum* yeast in tissue or sterile body fluid by cytopathology			O	O			

Detection in serum or cerebrospinal fluid (CSF) of *H. capsulatum* antibodies by single complement fixation titer of 1:32 or greater (e.g., 1:64)			O	O			
Detection in serum or cerebrospinal fluid (CSF) of M band by *H. capsulatum* immunodiffusion antibody test without a previous negative test			O	O			
Detection of *H. capsulatum* antigen in serum, urine, or other body fluid by an enzyme immunoassay test			O	O			
Epidemiologic Evidence							
Epidemiologically linked to a confirmed case						N	N
Criteria to distinguish a new case							
At least 24 months have lapsed since last reported onset of histoplasmosis in same individual	N	N	N	N	N	N	N
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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 (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case. (These "O" criteria are alternatives, which mean that a single column will have either no O criteria or multiple O criteria; no column should have only one O.) A number following an "O" indicates that this criterion is only required for a specific disease/condition subtype.

VIII. Period of Surveillance

Surveillance should be on-going.

IX. Data sharing/release and print criteria

Data will be used to monitor trends of histoplasmosis over time. Data may also be used to compare histoplasmosis cases across jurisdictions.

Information may be distributed among states and territories or to CDC depending on the current epidemiologic situation or jurisdiction specific protocols. Unusual situations may increase the need for communication. Frequency of cases, epidemiologic distribution, and other factors will influence communications.

States and territories will share data with CDC according to jurisdiction specific protocols.

State-specific data on cases, if shared with CDC, will be verified before publication.

X. Revision History

None.

XI. References

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