



Histoplasmosis Investigation Guideline

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Histoplasmosis

Disease Management and Investigative Guidelines

CASE DEFINITION (CDC 2017)

Clinical Description for Public Health Surveillance:

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 for Case Classification:

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,
- Demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen using a validated assay (i.e., polymerase chain reaction (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,
- 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.

Criteria to Distinguish a New Case from an Existing Case

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

Case Classification:

Probable:

- 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.*

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

LABORATORY ANALYSIS

Histoplasma antigen detection in urine and/or serum is the most widely used and most sensitive method for diagnosing disseminated histoplasmosis and acute pulmonary histoplasmosis following exposure to a large inoculum. Other methods include antibody tests, culture, and microscopy.

Because development of antibodies to *Histoplasma* can take two to six weeks, antibody tests are not as useful as antigen detection tests in diagnosing acute histoplasmosis or in immunosuppressed persons, who may not mount a strong immune response.

Serologic Test	Relative Diagnostic Value
Enzyme immunoassay (EIA)	<ul style="list-style-type: none"> Antigen detection performed on urine, serum, cerebrospinal fluid (CSF), or bronchoalveolar lavage fluid.
Complement fixation (CF)	<ul style="list-style-type: none"> Complement-fixing antibodies may take up to 6 weeks to appear after infection. CF is more sensitive but less specific than immunodiffusion
Immunodiffusion (ID)	<ul style="list-style-type: none"> Tests for the presence of antibodies to H (indicates chronic or severe acute infection) and M (develops within weeks of acute infection and can persist for months to years after the infection has resolved) precipitin bands; ~80% sensitivity.
Culture	<ul style="list-style-type: none"> Performed on tissue, blood, and other body fluids, but may take up to 6 weeks to become positive; most useful in the diagnosis of the severe forms of histoplasmosis. Confirm with a commercially available DNA probe.
Microscopy	<ul style="list-style-type: none"> For detection of budding yeast in tissue or body fluids, low sensitivity, but can provide a quick proven diagnosis if positive
Polymerase Chain Reaction (PCR)	<ul style="list-style-type: none"> Detection of <i>Histoplasma</i> directly from clinical specimens is still experimental, but promising.

Unless authorized to send directly to CDC, all specimens should be sent through the Kansas Health and Environment Laboratory (KHEL).

- The medical provider treating the patient must contact KDHE at 1-877-427-7317 for specimen approval.
- The laboratory or person submitting the specimen **must** contact KHEL at 785-296-1653 or 785-296-1645 **before** sending any specimens.

Additional information on shipping specimens to CDC:

- Questions regarding testing, contact CDC-INFO at 800-232-4636.
- Information on sample submission, including the sample submission form (DASH Form 50.34) and shipping instructions can be found at: https://www.cdc.gov/fungal/lab_submission.html.

EPIDEMIOLOGY

Histoplasma, the fungus that can cause histoplasmosis, lives in the environment, particularly in soil that contains large amounts of bird or bat droppings. In the United States, *Histoplasma* mainly lives in the central and eastern states, especially areas around the Ohio and Mississippi River valleys. The fungus also lives in parts of Central and South America, Africa, Asia, and Australia.

Those at risk are people in endemic areas, particularly those who have occupations or participate in activities exposing them to soil that contains bird or bat droppings. Disseminated histoplasmosis is more likely to occur in immunosuppressed persons (HIV/AIDS, organ transplant, or use of immunosuppressive medications), infants, or adults age 55 years and older.

DISEASE OVERVIEW (Source: CDC, [Information for Healthcare Professionals](#))

A. Agent:

Histoplasma capsulatum var. *capsulatum* (near-worldwide distribution) and *Histoplasma capsulatum* var. *duboisii* (in Africa)

B. Clinical Description:

Severity of illness depends on host immunity and the intensity of the exposure. Acute pulmonary histoplasmosis is often self-limiting; symptoms include fever, malaise, cough, headache, chest pain, chills, and myalgias. Persons with a history of pulmonary disease can develop chronic pulmonary histoplasmosis. Immunosuppressed persons are at risk of disseminated histoplasmosis.

C. Reservoirs:

Soil, particularly when heavily contaminated with bird or bat droppings.

D. Mode(s) of Transmission:

Histoplasmosis is typically acquired via inhalation of airborne microconidia, often after disturbance of contaminated material. Primary cutaneous histoplasmosis and solid organ donor-derived histoplasmosis are extremely uncommon.

E. Incubation Period:

Primary infection, 3 to 17 days after exposure.

F. Period of Communicability:

No direct person-to-person or animal-to-human transmission.

G. Susceptibility and Resistance:

Infection results in partial immunity; reinfection can occur but requires a larger inoculum. In people with weakened immune systems, histoplasmosis may relapse months or years later.

H. Treatment:

Mild to moderate cases of acute pulmonary histoplasmosis will often resolve without treatment; however, treatment is indicated for moderate to severe acute pulmonary, chronic pulmonary, disseminated, and central nervous system (CNS) histoplasmosis. Antifungal agents proven to be effective are amphotericin B

(including liposomal and lipid formulations) and itraconazole (for mild-to-moderate infections and step-down therapy). For more detailed treatment guidelines, please refer to the IDSA's [Clinic Practice Guidelines for the Management of Patients with Histoplasmosis](#).

NOTIFICATION TO PUBLIC HEALTH AUTHORITIES

Suspected cases of histoplasmosis shall be reported within 24 hours, except if the reporting period ends on a weekend or state-approved holiday, the report shall be made by 5:00 p.m. on the next business day after the 24-hour period.

1. Health care providers and hospitals: report to local health jurisdiction
2. Laboratories: report to KDHE - BEPHI
3. Local health jurisdiction: report to KDHE - BEPHI

**Kansas Department of Health and Environment (KDHE)
Bureau of Epidemiology and Public Health Response (BEPHI)**

Phone: 1-877-427-7317

Fax: 1-877-427-7318

Further responsibilities of state and local health departments to the CDC:

As a nationally notifiable condition, histoplasmosis cases require a ROUTINELY NOTIFIABLE report to the Center of Disease Control and Prevention (CDC).

1. ROUTINE reporting requires KDHE-BEPHI to file an electronic report for within the next reporting cycle. KDHE-BEPHI will file electronic reports weekly with CDC.
2. **Local public health jurisdiction** will report information requested in the Kansas electronic surveillance system, as soon as possible.

INVESTIGATOR RESPONSIBILITIES

- 1) [Report](#) all confirmed, probable and suspect cases to the KDHE.
- 2) The goal of the [case investigation](#) is to collect epidemiological data as required by current surveillance objectives.
 - Contact the medical provider to collect information needed confirm diagnosis using the current case definition.
 - The [Histoplasmosis Investigation Worksheet](#) will help in the confirmation of the case and with the organization and the collection of essential data
 - Collect all information requested in the case investigation.
 - Most data can be collected from the medical provider, and the patient may not need to be contacted.
- 3) Routine contact investigation is not needed for cases of histoplasmosis.
- 4) [Record](#) data, collected during the investigation, in the KS EpiTrax system under the data's associated **[tab]** in the case morbidity report (CMR) or by attaching scanned records.

STANDARD CASE INVESTIGATION AND CONTROL METHODS

Case Investigation

- 1) Contact the medical provider who ordered testing of the case and obtain the following information. (This includes medical records for hospitalized patients.)
 - Use the [Histoplasmosis Investigation Worksheet](#) to identify any symptoms of histoplasmosis, record onset date and symptoms experienced.
 - Examine the laboratory testing that was done to ensure all testing that could confirm the case has been reported. Obtain, scan, and attach copies of any lab reports that may still be needed to the EpiTrax record.
 - Collect case's demographic data and contact information (birth date, county, sex, race/ethnicity, occupation, address, phone number(s))
 - For females, record pregnancy status.
 - Record hospitalizations: location, admission and discharge dates
 - Obtain the reason for testing:
 - Was the patient exposed to bird or bat droppings?
 - Did the patient report any at-risk activities to the medical provider?
 - Record pre-existing medical conditions present at the time of onset.
 - Record outcomes: recovery, or date of death
- 2) Interview the case, proxy, or use medical record to determine source and risks.
 - Occupation or activities that may have resulted in exposure to bird or bat droppings.
 - Travel outside of the current county 3 days to 3 weeks prior to acute onset.

Contact Investigation

Usually none required. Provide education as needed.

Isolation, Work and Daycare Restrictions

None required for humans.

Case Management

Follow-up if case had not yet recovered, since last contact. Report any changes in case status (i.e. death).

Contact Management

Usually none required. Provide education as needed.

Environmental Measures

Large amounts of bird or bat droppings should be cleaned up by professional companies that specialize in the removal of hazardous waste.

The document, [Histoplasmosis: Protecting Workers at Risk](#), should be consulted before starting a job or activity where there is a possibility of being exposed to histoplasma.

Education

People with weakened immune systems should avoid doing activities that are known to be associated to histoplasmosis, including:

- Disturbing material where there are bird or bat droppings,
- Cleaning chicken coops,
- Exploring caves, and
- Cleaning, remodeling, or tearing down old buildings.

Counsel those exposed to the same source as a case, as follows:

- Symptomatic persons exposed to the same source should be strongly urged to contact their physician for a medical evaluation.
- Non-symptomatic persons with possible exposures should watch for symptoms for a period of 3 weeks.
- Immunosuppressed persons should be referred to a medical provider to determine if prophylaxis is necessary.

MANAGING SPECIAL SITUATIONS

A. Reported Incidence Is Higher than Usual/Outbreak Suspected:

- If you suspect an outbreak, consult with the epidemiologist on call at KDHE by calling the reporting hotline at 1-877-427-7318.

DATA MANAGEMENT AND REPORTING TO THE KDHE

- A. Accept the case assigned to the LHD and record the date the LHD investigation was started on the **[Administrative]** tab.
- B. Organize and collect data.
- The [Histoplasmosis Investigation Worksheet](#) is provided to assist the investigator but can be attached to the record in EpiTrax.
 - Investigators can also collect and enter all required information directly into EpiTrax **[Clinical]**, **[Demographics]**, **[Epidemiological]**, and **[Notes]** tabs without using the paper forms.
 - During outbreak investigations, refer to guidance from a KDHE epidemiologist for appropriate collection tools.
- C. Report data collected during the investigation via EpiTrax.
- Verify that all data requested in [Histoplasmosis Investigation Worksheet](#) has been recorded on an appropriate EpiTrax **[tab]**, or that actions are completed for a case lost to follow-up as outlined below.
 - Some data that cannot be reported on an EpiTrax **[tab]** may need to be recorded in **[Notes]** or scanned and attached to the record.
 - Paper report forms do not need to be sent to KDHE after the information is recorded in EpiTrax. The forms should be handled as directed by local administrative practices.
- D. If a case is lost to follow-up, after the appropriate attempts:
- Indicate 'lost to follow-up' on the **[Administration]** tab with the number of attempts to contact the case recorded.
 - Record at least the information that was collected from the medical records.
 - Record a reason for 'lost to follow-up' in **[Notes]**.
- E. Once the investigation is completed, the LHD investigator will click the "Complete" button. This will trigger an alert to the LHD Administrator, so they can review the case before sending to the state.
- The LHD Administrator will then "Approve" or "Reject" the CMR.
 - Once a case is "Approved" by the LHD Administrator, BEPHI staff will review the case to ensure completion before closing the case.

Review the [EpiTrax User Guide, Case Routing](#) for further guidance.

ADDITIONAL INFORMATION / REFERENCES

- A. Treatment / Differential Diagnosis:** American Academy of Pediatrics. Red Book: Report of the Committee on Infectious Disease, 29th Edition. Illinois, Academy of Pediatrics, 2014.
- B. Epidemiology, Investigation and Control:** Heymann. D., ed., Control of Communicable Diseases Manual, Washington, DC, American Public Health Association, 2010.
- C. Case Definitions:** www.cdc.gov/nndss/
- D. Kansas Regulations/Statutes Related to Infectious Disease:** www.kdheks.gov/epi/regulations.htm
- E. Infectious Diseases Society of America (IDSA):**
- Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: <https://academic.oup.com/cid/article/45/7/807/541502>
- F. Additional Information (CDC):**
- Biosafety in Laboratories: https://www.cdc.gov/biosafety/publications/bmbl5/BMML5_sect_VIII_b.pdf
 - National Institute for Occupational Safety and Health (NIOSH): <https://www.cdc.gov/niosh/docs/2005-109/>
 - <https://www.cdc.gov/fungal/diseases/histoplasmosis/index.html>

Histoplasmosis Investigation Worksheet

Patient Name Last:		First:			Middle:		
Date of Birth:	Sex: <input type="checkbox"/> Male <input type="checkbox"/> Female		Pregnant:	Yes	No	Unk	
If pregnant, trimester:							

Ethnicity/Race (mark one or more)

<input type="checkbox"/> Hispanic or Latino	<input type="checkbox"/> American Indian/ Alaska Native	<input type="checkbox"/> Asian	<input type="checkbox"/> Black or African American	<input type="checkbox"/> Other
<input type="checkbox"/> Not Hispanic or Latino	<input type="checkbox"/> Native Hawaiian / Other pacific islander	<input type="checkbox"/> Filipino	<input type="checkbox"/> White	<input type="checkbox"/> Unknown

Histoplasmosis Symptoms

Onset Date:				Cough			Yes	No	Unk	Myalgia			Yes	No	Unk
Fever	Yes	No	Unk	Chest Pain			Yes	No	Unk	Rash: Erythema nodosum			Yes	No	Unk
Headache	Yes	No	Unk	Shortness of Breath			Yes	No	Unk	Rash: Erythema multiforme			Yes	No	Unk

Abnormal Chest Imaging:

<input type="checkbox"/> Not done	<input type="checkbox"/> Pulmonary infiltrates	<input type="checkbox"/> Enlarged hilar or mediastinal lymph nodes	<input type="checkbox"/> Other:
	<input type="checkbox"/> Cavitation	<input type="checkbox"/> Pleural infusion	

Clinical Evidence of Disseminated Disease:

<input type="checkbox"/> Gastrointestinal ulcerations or masses	<input type="checkbox"/> Pancytopenia (evidence of bone marrow involvement)
<input type="checkbox"/> Skin or mucosal lesions	<input type="checkbox"/> Enlargement of the liver, spleen, or abdominal lymph nodes
<input type="checkbox"/> Peripheral lymphadenopathy	<input type="checkbox"/> Meningitis, encephalitis, or focal brain lesion

Existing Medical Conditions (check all present at the time of disease onset):

<input type="checkbox"/> Asthma	<input type="checkbox"/> COPD/emphysema	<input type="checkbox"/> Immunocompromised	<input type="checkbox"/> Tuberculosis
<input type="checkbox"/> Cancer (type): _____	<input type="checkbox"/> Corticosteroid	<input type="checkbox"/> Organ Recipient	<input type="checkbox"/> Other:
<input type="checkbox"/> Chemotherapy	<input type="checkbox"/> Diabetes	<input type="checkbox"/> Smoker	

Travel History:

Did the patient travel outside of the county of residence 3-days to 3-weeks prior to onset?	Yes	No	Unk
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If yes specify locations below.

Location (City, County, State, Country)	Date Travel Started	Date Travel Ended

Occupation and activity assessment on page 2.

Histoplasmosis Investigation Worksheet

Patient occupation(s) during 3 weeks prior to onset	Address of employer or school	Dates
1.		
2.		
3.		

Was the patient exposed to any of the following situations during the 3 weeks before onset of illness?

	Yes	No	Unk	When/Where:
Accumulated bat or bird manure				
Attic/barn/chimney cleaning				
Bridge inspection				
Cave interior work or spelunking				
Construction/Demolition work				
Heating and AC installation				
Gardening/landscaping				
Handling /raising birds				
Lawn care (raking, mowing)				
Visiting a cabin				
Camping				
Other outdoor activities:				