Coccidioidomycosis

Signs and Symptoms	• Most infections asymptomatic (~60%) • Typical symptoms include fever, cough, fatigue, shortness of breath, headache, pneumonia or pulmonary lesion (5-10%), erythema nodosum or erythema multiforme • ~1% disseminated disease (bone, joint, skin, meninges, viscera or lymph node); dissemination more likely for men, some racial groups, altered immune system	
Incubation	1-3 weeks. Reactivation and dissemination may occur after years.	
Case classification	**Clinical criteria**: Influenza-like illness (ILI), pneumonia or pulmonary lesion, erythema nodosum or erythema multiforme, or disseminated infection.	
	Laboratory criteria: *Confirmatory* - Culture, identification by histopathology, nucleic acid, MALDI-ToF, antibodies in CSF or antibodies in serum with specific assays *Presumptive* – antibodies in serum with specific assays, antigen detection	
	Confirmed: Meets confirmatory lab and either clinical criteria or epi link; OR presumptive lab and both clinical and epi link	**Probable:** Meets confirmatory lab but not epi link or clinical criteria; OR presumptive lab and either clinical criteria or epi link
Differential diagnosis	Actinomycosis, aspergillosis, blastomycosis, community acquired pneumonia, cryptococcosis, histoplasmosis, meningitis, sarcoidosis, tuberculosis, malignancy	
Treatment	Antifungal agents can be given, particularly for debilitating or disseminated disease. See IDSA treatment guidelines. Rare deaths.	
Duration	Usually self-limiting, although those with progressive, chronic, or disseminated disease can experience symptoms for months or longer. Disease can recur. No person-to-person or animal-to-person transmission.	
Exposure	Inhalation of fungal spores from dust or disturbed soil (construction, farm work, field training, recreation, dust storm, earthquake). Cultures should be handled with BSL2.	
Laboratory testing	Local Health Jurisdiction (LHJ) and Communicable Disease Epidemiology (CDE) arrange testing for individual cases and environmental testing for suspected outbreaks. Isolates should be submitted for genotyping. • Washington State Public Health Laboratories can facilitate testing at CDC • **Best specimens**: **Fungal isolate**; testing can be arranged for sera, CSF, pleural fluid, synovial fluid, or ascitic fluid *Specimen shipping (Section 4):* • Isolates **must** be submitted on a slant with a screw top. Petri dishes are **not** acceptable Keep isolate at room temperature, clinical specimens cold, ship according to PHL requirements: https://doh.wa.gov/public-health-provider-resources/public-health-laboratories/lab-test-menu • Specimen Collection and Submission Instructions: https://www.cdc.gov/fungal/lab-professionals/sample-submission.html	
Public health actions **URGENT**	Immediately report to CDE any potential laboratory exposure to cultures. • Identify immunocompromising conditions (e.g. HIV infection, organ transplantation, malignancy, pregnancy) that might affect treatment decisions • Identify likely region of exposure, particularly if within Washington State Identify and evaluate laboratory personnel handling a *Coccidioides* culture and obtain baseline serum sample for possible later testing if symptoms develop. Recommend 6 weeks of anti-fungal prophylaxis and symptom watch for those exposed. *Infection Control:* standard precautions.	

Coccidioidomycosis

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To track the emergence of *Coccidioides* in Washington.
2. To differentiate between infection acquired in Washington versus disease acquired outside of Washington.
3. To monitor trends in the epidemiology of disease due to *Coccidioides*.

B. Legal Laboratory Reporting Requirements

1. **Health care providers** and **Health care facilities**: notifiable to **local health jurisdiction** within 3 business days.
2. **Laboratories**: notifiable to **local health jurisdiction** within 2 business days; submission required – isolate, within 2 business days; if no isolate available, on request specimen associated with a positive result, within 2 business days.
3. **Veterinarians:** animal cases notifiable to Washington State Department of Agriculture https://app.leg.wa.gov/WAC/default.aspx?cite=16-70
4. **Local health jurisdictions:** notifiable to the Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE) within 7 days of case investigation completion or summary information required within 21 days.

C. Local Health Jurisdiction Investigation Responsibilities

1. Identify potential travel-related or local exposures.
2. When possible, request medical records for completion of supplemental CDC case report form. (Note: CDE will assist in completing the supplemental form).
3. Facilitate transport of specimens to the Washington State Public Health Laboratories (PHL). Please call CDE prior to submitting specimens (206-418-5500 or 877-539-4344).
4. Report all *confirmed* and *probable* cases to CDE (see definition below). Complete the coccidioidomycosis case report form https://www.doh.wa.gov/Portals/1/Documents/5100/420-123-ReportForm-Cocci.pdf and enter the data in the Washington Disease Reporting System (WDRS).

2. THE DISEASE AND ITS EPIDEMIOLOGY

Background

Coccidioides (spp. *immitis* or *posadasii*) is an environmental fungus that grows in soil in areas of low rainfall, high summer temperatures and moderate winter temperatures. *Coccidioides* was previously known to occur only in the Southwestern United States and parts of Mexico and Central and South America. Infection with *Coccidioides,* called coccidioidomycosis or more commonly, Valley Fever, is frequently reported from these areas; over 95% of US cases have been reported from Arizona and California. A sharp increase in case incidence in endemic regions of California was reported in 2016

following a four-year decline, potentially due to changes in environmental conditions favorable to *Coccidioides* proliferation and airborne release. *Coccidioides immitis* was first recognized as a locally occurring pathogen in Washington State in 2010, when two human cases with no or limited travel history were diagnosed in south-central Washington. Several soil samples collected from south-central Washington have also tested positive for the fungus, and specimens from one site were indistinguishable from clinical isolates of one case by whole genome sequencing. Disease can occur in humans and domestic and wild animals (dogs, cats, rodents, etc.).

A. Etiologic Agent

Coccidioides spp. are dimorphic ascomycetes that dwell in the soil. *Coccidioides immitis* is typically found in California, parts of Mexico, and recently in Washington, whereas *Coccidioides posadasii* is generally found in Arizona and other areas of the Southwest. Geographic ranges for *Coccidioides* spp. are still not fully understood, but genotypes are known to vary by region. Clinical differences between the two species have not been observed. The *Coccidioides* lifecycle depends on changes in climate; the fungal mycelia require moisture in the soil to grow. The hyphae need a period of dryness to promote desiccation and maturation into fungal spores (arthroconidia), which can be aerosolized and inhaled. Within the lung, the spore changes into a multi-cellular spherule. Both weather patterns and soil composition therefore appear to affect *Coccidioides* infection rates.

B. Description of Illness

Many infections are sub-clinical, with no symptoms or mild flu-like symptoms. Approximately 40% of infections are symptomatic; these cases generally present with fever, fatigue, cough, dyspnea, headache, night sweats, myalgias, and rash. Some people may develop erythema nodosum or erythema multiforme. Primary pulmonary disease is often self-limiting, but some patients fail to recover and develop complications or chronic pulmonary disease, including lung nodules (5-10% of cases). Disseminated disease occurs in about 1% of cases, with bones/joints, soft tissues, and central nervous system most commonly affected. Men have a higher rate of dissemination than women, and several studies indicate that African Americans and Filipinos are also at higher risk. Increased risk of dissemination also occurs for persons with immune system alterations such as with HIV infection, diabetes, pregnancy, organ transplants, Hodgkin's disease, or chronic corticosteroid therapy.

C. *Coccidioides immitis* in Washington State

In 1997, a dog from King County with no known out-of-state travel but travel to Yakima County was diagnosed with *Coccidioides* infection by culture. Documentation of similar cases includes a horse from Asotin County in 1999 and a dog with unknown residence in 2000.

Between June 2010 and May 2011, physicians in Washington diagnosed three unrelated cases of acute coccidioidomycosis in south-central Washington residents without recent travel to known endemic areas. Soil samples were collected from suspected exposure sites, and the genotype of one environmental isolate was identical to a clinical isolate from one patient by whole genome sequencing. This provided direct evidence that the

infections were acquired in Washington and that *C. immitis* exists in the state's environment. As of December 2022, a total of 20 confirmed cases with suspected or confirmed Washington exposure have been identified, all with exposure in eastern Washington.

D. Reservoirs

Coccicioides grows in soil, and fungal spores can become airborne when the soil is disturbed by winds, construction, farming, and other activities. Possible animal reservoirs, such as the kangaroo rat and the Arizona pocket mouse, have been proposed, but no zoonotic transmission to humans has been reported.

E. Modes of Transmission

Infection occurs when a fungal spore is inhaled, generally from dust or disturbed soil (e.g. construction, farming, field training, digging, dust storm, dust-raising recreational activities, or earthquake). Infection can occur from laboratory handling of cultures outside of appropriate biosafety areas. BSL-2 practices, containment equipment, and facilities are recommended for handling and processing clinical specimens, identifying isolates, and processing animal tissues. BSL-3 practices, containment equipment, and facilities are recommended for propagating and manipulating sporulating cultures already identified as *Coccidioides* and for processing soil or other environmental materials. Laboratory exposures lead to a much higher rate of clinical disease than natural exposures; presumably due to higher infectious dose. There is no person-to-person or animal-to-person transmission reported.

F. Incubation Period

One to three weeks. Latent or reactivation infection presenting months to years later can also occur in immunosuppressed persons; at least two published case reports indicate coccidioidomycosis reactivation can occur early after treatment for HIV infection, during the phase of recovery of the immune system.

G. Period of Communicability

Coccidioidomycosis is not transmitted person-to-person or from animals to humans.

H. Treatment

Coccidioidomycosis can be treated with antifungal therapy, particularly for debilitating disease. Treatment recommendations vary by immune status. See specific treatment guidance published by the Infectious Disease Society of America (2016): https://academic.oup.com/cid/article/63/6/e112/2389093

3. CASE DEFINITIONS

A. Clinical Criteria for Diagnosis

In the absence of a more likely diagnosis of an alternative fungal infection, such as histoplasmosis or blastomycosis, which have similar clinical presentation as coccidioidomycosis, and which can lead to serologic and antigenic false positives for coccidioidomycosis due to cross-reactivity:

- Acute onset or worsening of at least two of the following signs or symptoms:

- Cough
- Fever or chills or night sweats
- Shortness of breath
- Chest or flank pain
- Headache
- Unintentional weight loss
- Myalgia (muscle pain)
- Arthralgia (joint pain) or bone pain
- Fatigue,

OR

- At least one of the following findings:
  - Abnormal lung findings on chest imaging (e.g., pulmonary infiltrates, nodule, or cavitary lesions) or report of pneumonia
  - Single or multiple skin lesions
  - Bone or joint abnormality (e.g., osteomyelitis, pathologic fracture)
  - Meningitis, encephalitis, or focal brain lesion
  - Abscess, granuloma, or lesion in other body system
  - Erythema nodosum or erythema multiforme rash.

B. Laboratory Criteria for Diagnosis

1. Confirmatory laboratory evidence:
   - Culture of Coccidioides spp. from a clinical specimen, OR
   - Identification of characteristic Coccidioides spp. in tissue or body fluid by histopathology, OR
   - Identification of characteristic Coccidioides spp. in tissue or body fluid by cytopathology, OR
   - Detection of Coccidioides-specific nucleic acid in a clinical specimen using a validated molecular assay (e.g., PCR, DNA Probe), OR
   - Detection of Coccidioides-specific proteins in a clinical specimen or isolate using a validated molecular assay (e.g., MALDI-TOF), OR
   - Detection of coccidioidal antibodies in cerebrospinal fluid (CSF), OR
   - Detection of coccidioidal antibodies in serum or other body fluids using any of the following diagnostic tests:
     - Immunodiffusion (may be abbreviated as ID, IMD, IMDF, IDTP, IDCF)
     - Complement fixation (CF) with a titer of >1:2

- Tube precipitin
- Detection of both IgM and IgG by enzyme immunoassay (may be abbreviated as EIA or ELISA).

2. Presumptive laboratory evidence:

- Detection of coccidioidal antibodies in serum or other body fluids using any of the following diagnostic tests:
  - Complement fixation (CF) with a titer of 1:2
  - Lateral flow assay (LFA)
  - Latex agglutination
  - Detection of either IgM or IgG by enzyme immunoassay (may be abbreviated as EIA or ELISA), OR
- Detection of Coccidioides spp. antigen in serum, urine, CSF, or other body fluids.

C. Epidemiologic Linkage

Exposure to a Coccidioides spp. endemic area, including via residence, work, or travel, in the 2 months prior to acute symptom onset or positive coccidioidal laboratory result if acute onset date is unknown.

To assess areas of endemicity, investigators can reference CDC's estimated areas with Coccidioides spp. (https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html). Current estimates of where Coccidioides spp. live are based on public health surveillance data, outbreak locations, skin testing studies, and detection of Coccidioides spp. in the environment.

Of note, it can be challenging and complex to determine the Coccidioides spp. endemicity of a specific area, and endemicity is expected to change and likely expand over time, particularly given the influences of climate change. Investigators can work with public health officials in the state where exposure may have occurred to make a determination if epidemiologic linkage criteria are met.

If exposure history is not available, assume the case does not meet the epidemiologic linkage criteria.

D. Case classification (2023)

For classification purposes, Washington State is defined as a low-incidence jurisdiction

Confirmed*:

- A case that meets confirmatory laboratory evidence AND either epidemiologic linkage OR clinical criteria, OR
- A case that meets presumptive laboratory evidence AND epidemiologic linkage AND clinical criteria.

Probable*:

- A case that meets confirmatory laboratory evidence and does NOT meet epidemiologic linkage criteria AND does NOT meet clinical criteria, OR

- A case that meets presumptive laboratory evidence AND either epidemiologic linkage OR clinical criteria.

Suspect*:

- A case that meets presumptive laboratory evidence and does NOT meet epidemiologic linkage criteria AND does NOT meet clinical criteria.

*Illness in a person with compelling evidence (e.g., culture, histopathology, seroconversion) of a different fungal infection, such as histoplasmosis or blastomycosis, should not be counted as a case of coccidioidomycosis without evidence of co-infection since other fungal infections can cause false positive (cross-reactive) Coccidioides spp. antigen and antibody test results. Thus, coccidioidomycosis cases should only be classified as such in the absence of a more likely diagnosis.

Criteria to distinguish a new case: A new case is a case not known to be previously reported and counted in any public health jurisdiction in the United States. If it is known that a case was previously diagnosed or reported out-of-state, that case should not be counted or reported again.

Reactivation of coccidioidomycosis can occur, particularly among patients with previous coccidioidomycosis who are later treated with immunosuppressive medications. Potential cases of reactivation should not be counted or reported unless they are known to have not been previously diagnosed or reported. Multiple cases of coccidioidomycosis for the same patient should only be reported if reactivation of a previous infection can be ruled out (i.e., patient was reinfected) by whole genome sequencing (i.e., sequencing data indicate infection from distinct Coccidioides spp. lineages/strains).

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

Recommended commercially available tests to aid in the diagnosis of coccidioidomycosis include: serology, histopathology with special stains, PCR, MALDI-ToF, antigen tests, or fungal culture. IgM antibodies are detectable in ~50% of patients by one week after symptom onset and ~90% by 3 weeks after symptom onset. IgG antibodies are generally detectable by 4-6 weeks post symptom onset, and ~85-90% of patients have detectable IgG by 3 months. However, antibodies generally do not persist longer than several months to a year, occasionally longer in association with a pulmonary cavity or disseminated disease. All serology is generally considered acute testing and a marker for current or recent infection. While false positives are rare, false negatives may occur in up to a third of confirmed cases. Therefore, negative serologic results do not rule out coccidioidal disease. One study reported approximately 5% of immunocompromised patients with coccidioidomycosis are seronegative.

Cerebrospinal fluid (CSF) should be tested for patients with suspected or diagnosed meningitis. Fungal culture can be performed from respiratory secretions (sputum, BAL), normally sterile fluids (e.g., pleural, peritoneal), tissues (fine needle aspirates or biopsies of the lung, brain, skin), or abscesses. If an isolate is available, submit to PHL to be forwarded to CDC for sequencing. Sequencing can determine if the strain matches or is

similar to other strains isolated in south-central Washington or if it is similar to strains found in the Southwest United States.

A positive skin test (spherulin) indicates prior exposure and infection with the fungus. Because reactivity is lifelong, skin tests are not generally helpful in diagnosing current infection, but can help determine whether a person is at risk of infection.

Whole genome sequencing of the organism provides useful information to help determine likely geographic region of exposure.

B. Testing Available at Washington State Public Health Laboratories (PHL)

PHL currently offers EIA testing for *Coccidioides.* In general, testing should be first performed at commercial laboratories, but in special situations of suspected outbreaks or unavailability of testing, testing at PHL will be approved.
In addition, PHL will facilitate transfer of isolates or other specimens for special study to the Centers for Disease Control and Prevention (CDC) for confirmation of species and for genotyping. **Please submit any available clinical isolates to PHL.** Isolates should be sent on slants (room temperature). Petri dishes and paraffin blocks are not accepted. Submit serum or tissue slides to be forwarded to CDC according to PHL requirements: https://doh.wa.gov/public-health-provider-resources/public-health-laboratories/lab-test-menu
Serum specimens to be tested at PHL should be submitted according to PHL requirements: https://doh.wa.gov/public-health-provider-resources/public-health-laboratories/lab-test-menu

Note that PHL require all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

In specific situations, other specimens such as pleural fluid, synovial, or ascetic fluid can be tested through the UC Davis Coccidioidomycosis Laboratory; consult with the laboratory and CDE about the case prior to submitting specimens.

5. ROUTINE CASE INVESTIGATION

Interview the case and others who might provide pertinent information. Obtain medical records if possible.

A. Evaluate the Diagnosis

Review the clinical presentation and use the case report form to record signs and symptoms. Collect information on whether the patient was hospitalized, date of onset of symptoms thought to be caused by coccidioidomycosis, and any underlying diseases, especially immunocompromising conditions such as HIV infection or organ transplantation. Get copies of laboratory reports that support the diagnosis. Since genotyping is often recommended, secure the isolate if available, and submit to PHL.

B. Identify Source of Infection

Ask about recent travel and outdoor activity during the past month, particularly in the Southwestern United States, Mexico, Central or South America, or eastern Washington.

In cases without recent reported travel to a known endemic area, ask about lifetime travel history to these areas, and consult Office of Communicable Disease Epidemiology about possible in-state acquired cases.

C. Identify Potentially Exposed Persons

Identify others potentially exposed in the same setting as the case, and ask about flu- or pneumonia-like illness following exposure. Identify and evaluate laboratory personnel handling a *Coccidioides* culture. If a *Coccidioides* culture was handled outside of a biological safety cabinet, a list of all persons present in the room should be collected. See section 6B for management of exposed laboratory personnel.

D. Environmental Evaluation

Notify Communicable Disease Epidemiology of suspected locally acquired cases. In some cases, further environmental investigation may be recommended.

E. Infection Control Recommendations

1. Hospitalized patients should be cared for using standard precautions.
    a. Risk of respiratory infection from exposure to infected tissue or aerosols of infected secretions is very low.
    b. Accidental percutaneous inoculation has typically resulted in local granuloma formation.
2. There is no need for patient isolation or work/day care restrictions.

6. MANAGING SPECIAL SITUATIONS

A. *Coccidioides* in an Animal

Consult with the DOH Zoonotic Disease Program (360-236-3385) regarding infections in animals. Confirmatory testing and genotyping are also available at the Centers for Disease Control and Prevention (CDC). Isolates should be submitted to Washington State Public Health Laboratories. If possible, obtain veterinary records for review, interview the owner regarding pet environment and potential exposure locations, and consider environmental sampling.

B. *Coccidoides* exposure in a laboratory

If a *Coccidioides* culture is handled outside of a biological safety cabinet, a list should be made of everyone present in the room at the time of exposure. A baseline serum sample should be obtained promptly from persons exposed to *Coccidioides* and these samples should be stored for eventual testing if symptoms develop. These tests may help determine whether there was any prior exposure to *Coccidioides.* All persons deemed to have been exposed should be given a therapeutic dose of either itraconazole or fluconazole orally for 6 weeks, as prophylaxis. During this 6 week period, all exposed persons should be on symptom watch. If illness develops, they should present to a clinician for diagnostic testing. A second serum specimen should be collected 3-12 weeks after symptom onset for comparison with the baseline specimen. See specific recommendations published by Clinical Infectious Diseases (2009): https://academic.oup.com/cid/article/49/6/919/334683

7. ROUTINE PREVENTION

A. Immunization Recommendations

A coccidioidomycosis vaccine is not currently available.

B. Prevention Recommendations

Avoid dusty environments or engaging in activities that disrupt soil in risk areas. Be alert for symptoms and consult a health care provider for early diagnosis and treatment.

ACKNOWLEDGEMENTS

This document is a revision of the Washington State Guidelines for Notifiable Condition Reporting and Surveillance published in 2002 which were originally based on the Control of Communicable Diseases Manual (CCDM), 17th Edition; James Chin, Ed. APHA 2000. We would like to acknowledge the Oregon Department of Human Services for developing the format of this document.

Resources:

- https://vfce.arizona.edu/
- https://academic.oup.com/cid/article/63/6/e112/2389093
- https://academic.oup.com/cid/article/49/6/919/334683
- https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6320a3.htm
- https://www.cdc.gov/mmwr/volumes/66/wr/mm6631a4.htm

UPDATES

March 2015: First issued guideline for *Coccidioides*.

December 2017: Routine update including new treatment guideline; front page added.

December 2022: Added 2023 CSTE case definition, routine updates, edited timeline for reporting per 2023 WAC updates.

December 2023: For 2024 WAC revision updated laboratory submission.