Cryptococcosis

Investigative Guidelines

May 2025

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To define the burden and to monitor trends of all cryptococcal infection in Oregon.
2. To determine the proportions of cryptococcal disease caused by *Cryptococcus neoformans* and *C. gattii.*
3. To identify risk factors for invasive *C. neoformans* and *C. gattii* infections.
4. To discern differences in outcomes of *C. neoformans* and *C. gattii* infections and other cryptococcal infections.

1.2 Laboratory and Physician Reporting Requirements

1. Health care providers, health care facilities and clinical laboratories are required to report cryptococcal infections to the local public health department within one local public health authority working day.
2. Licensed laboratories are required to submit cryptococcal isolates to the Oregon State Public Health Laboratory (OSPHL).

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed and presumptive cases to the Oregon Health Authority (OHA) by entry of data into Orpheus, within one working day of the initial physician or laboratory report.
2. Begin follow-up investigation within one working day. When possible, request medical records. Review and complete the relevant fields in Orpheus. Cases with non-invasive disease are confirmed, but should not be investigated.
3. Facilitate transport of cryptococcal isolates to the Oregon State Public Health Laboratory (503-693-4100).

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Cryptococcus spp. are environmental fungi. *C. gattii* was previously known as a fungus that was found in tropical or subtropical climates, but an environmental reservoir has recently been recognized in the Pacific Northwest. Animal and human cases appeared in an outbreak on Vancouver Island, British Columbia (BC), Canada, starting in 1999. The fungus has subsequently been found in environmental samples on Vancouver Island, mainland BC, Washington State,

and Oregon. *C. gattii* has caused illness among people as well as in domestic and wild animals, including dogs, cats, ferrets, horses, llamas, sheep, goats and porpoises. *Cryptococcus* spp. are saprophytic, encapsulated yeasts. They are Gram-positive and have a spheroid or ovoid shape. There are many species of *Cryptococcus*, but *C. neoformans* (varieties *neoformans* and *grubii*) and *C. gattii* are the primary human pathogens of this genus.

2.2 Description of Illness

Cryptococcal infection is thought to begin with inhalation of spores and infection of the lungs with resultant pneumonia; but it can disseminate to infect the central nervous system, presenting as meningitis. Untreated meningitis ends fatally in weeks to months. Reported symptoms depend upon the presentation, but may include headache, stiff neck, severe, prolonged cough (lasting weeks to months), shortness of breath, fever, chills, night sweats, and loss of appetite. Lung, brain, or muscle cryptococcomas (large mass lesions or nodules) may develop. The skin may show acneiform lesions, ulcers or subcutaneous tumor-like masses. Infection of the kidneys, prostate, and bone may also occur. The infection may become chronic, requiring long-term or life-long treatment. Occasionally, the causal agent may act as an endobronchial saprophyte in patients with other lung diseases. Asymptomatic infections may occur, with cryptococcomas identified on imaging studies done for other purposes.

Diagnosis of cryptococcal meningitis is aided by the evidence of encapsulated budding forms on microscopic examination of cerebral spinal fluid (CSF) mixed with India ink. Cryptococcal antigen (CrAg) tests in serum and CSF are helpful in establishing a preliminary diagnosis. Confirmation is via culture or histopathology.

Unfortunately, standard methods of diagnosis in clinical laboratories do not differentiate between *Cryptococcus gattii* and *C. neoformans.* Isolation of the organism in culture is needed for speciation. Cryptococcal isolates can be plated on chromogenic differential medium called Canavanine-Glycine-Bromothymol blue (CGB) agar, on which *C. gattii* will trigger a blue color reaction as it grows, whereas *C. neoformans* will not grow on CGB agar so that the medium remains yellow. False positive or false negative results may occur occasionally.

Genotyping of the organism, which has been done at CDC, can provide useful information about genetic relatedness and may help to link cryptococcal cases to the Pacific Northwest or other geographic locations.

Practice guidelines for Cryptococcal Disease can be found at:
https://www.idsociety.org/practice-guideline/cryptococcal-disease/

2.3 Reservoirs

C. gattii is an environmental fungus that has been isolated from native trees, soil, air, and water in the Pacific Northwest. In Australia, *C. gattii* can be found in

certain species of eucalyptus trees. *C. neoformans* has been consistently isolated from pigeon droppings.

***Cryptococcus gattii* in Oregon**

C. gattii infection was first diagnosed in Oregon in late 2004, and since then a number of human and animal cases have been reported. Since the exposure period can be long, determining exposure location may be difficult. Environmental sampling has also confirmed the presence of the fungus in Oregon.

2.4 Sources and Routes of Transmission

Presumably by inhalation of spores from the environment. *Cryptococcus* is not transmissible from person to person or from animal to person.

2.5 Incubation Period

Two to 13 months. Pulmonary disease may precede brain infection by months or years

2.6 Treatment

Typically, either amphotericin B plus 5-flucytosine or fluconazole alone is recommended. See specific anti-fungal treatment guidance published by the Infectious Diseases Society of America (2010): *www.idsociety.org/practice-guideline/cryptococcal-disease/*

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

An individual from whom *Cryptococcus* sp. is isolated or identified on histopathology.

3.2 Presumptive Case Definition

An individual with either clinical meningitis or pulmonary infection, and in whom cryptococcal antigen is detected in serum or cerebrospinal fluid.

3.3 Suspect Case Definition

A patient with a positive cryptococcal antigen only.

3.4 Services Available at the Oregon State Public Health Laboratory (OSPHL)

The Oregon State Public Health Laboratory (OSPHL) confirms *C. neoformans* and *C. gattii* isolates and forwards all isolates to the CDC for further characterization. All other *Cryptococcus* species will be forwarded to the CDC for additional fungal studies. Isolates should be sent at ambient temperatures on slants or on Agar plates supporting growth and tightly sealed with paraffin wrap. Paraffin blocks are not accepted. Complete acceptance criteria for isolate

submission can always be found on the OSPHL Lab Test Menu at www.healthoregon.org/labtests.

Serology, cryptococcal antigen testing and histopathologic examination are not available through OSPHL.

4. ROUTINE CASE INVESTIGATION

Patient interview and the medical record should provide most of the information needed for the disease investigation. Complete the fields in Orpheus regarding patient demographics, clinical information, laboratory data, risk factor information, and travel history. Ensure that any cryptococcal isolate is forwarded to OSPHL for speciation. Cases of invasive disease (brain, blood or respiratory infection) should always be investigated. Cases with non-invasive disease such as skin or nail infections with a cryptococcal-positive culture should be labeled as confirmed and not investigated any further.

4.1 Identify Source of Infection

Obtain history of any travel out of state during the putative incubation period. Note any "smoking gun" exposures — e.g., heavy exposure to sawdust or mulch.

4.2 Identify Other Potentially Exposed Persons

Not applicable.

4.3 Environmental Evaluation

Generally, not done. Consult ACDP regarding utility of environmental testing if a particular exposure is suspected based on history.

5. CONTROLLING FURTHER SPREAD

5.1 Infection Control Recommendation

None.

5.2 Isolation and Work or Day Care Restrictions

There is no need for patient isolation or restrictions on work or day care.

5.3 Follow-up of Cases

No follow-up needed.

5.4 Protection of Contacts

None, the infection is not spread person to person.

5.5 Environmental Measures

In general, none.

6. MANAGING SPECIAL SITUATIONS

Notify ACDP of any apparent clusters of cases.

UPDATE LOG

May 2025: Updated with minor changes and edits (DeBess, Beauchamp)

April 2018. Migrate document to new format, minor updates and review by OSPHL (DeBess, Humphrey).

January 2018. Added: Cases of invasive disease (brain, blood or respiratory infection) should always be investigated. Cases with no invasive disease such as skin or nail infections with a cryptococcal positive culture should be labeled as confirmed and not investigated any further, Section 4 (DeBess).

June 2013. Reviewed (DeBess and Cieslak)

December 2012. Created (DeBess)