Submission Date: 4/15/2014

Committee: Infectious Disease

Title: Standardized Surveillance Case Definition for Cryptococcus gattii infection

I. Statement of the Problem
Cryptococcal infections are caused by the environmentally ubiquitous fungus Cryptococcus neoformans and the related but less common species Cryptococcus gattii; infection by the latter is associated with one-year mortality rates of ~25%. It is thought that C. gattii infections require more prolonged, aggressive treatment than C. neoformans cryptococcosis [6], and the epidemiology of infections by the two species appear to differ as well. Cryptococcus gattii is an emerging pathogen in the United States, best known for having caused an outbreak in the Pacific Northwest [1], but locally acquired infections have been identified in several other states during the past five years [2-5]; however, with no standardized reporting, its geographic distribution within the United States is largely unknown.

II. Background and Justification
Cryptococcus is a ubiquitous fungal pathogen that causes primarily meningitis and pneumonia. The incidence of cryptococcal infection in the United States has been estimated at 0.4–1.3 cases/100,000/year. Two species of Cryptococcus cause the vast majority of human infections: C. neoformans and C. gattii. C. neoformans has a clear predilection for causing disease in persons in whom the immune system is impaired, and today an overwhelming proportion of C. neoformans infections occur in immunocompromised persons. In contrast, C. gattii was, until recently, considered a disease exclusive to immunocompetent persons living in tropical and subtropical regions of the world [8]. Early data from endemic areas suggested that C. gattii differed not only in epidemiology and clinical presentation from C. neoformans, but might also have different susceptibilities to antifungal agents [9-15] and require more aggressive and lengthier antifungal therapy than C. neoformans infections [16-20].

C. gattii and C. neoformans are easily differentiated by culture on commercially available (Hardy Diagnostics) chromogenic agar [7], and public health laboratories in states where C. gattii is reportable have acquired the capacity for this differentiation. However, where C. gattii is not reportable, cryptococcal infections are rarely identified to the species level, because commercially available automated identification systems (e.g., Vitek and Microscan) do not distinguish between species and by default report any cryptococcal isolate as C. neoformans. It is probable that most C. gattii infections are misdiagnosed as C. neoformans.

Before 1999, C. gattii infection was rarely reported in the United States or Canada [21-23]. A 1999 outbreak of C. gattii infection on Vancouver Island, British Columbia was notable for four factors: first, it was the first documented community outbreak of cryptococcosis; second, reports of C. gattii infections in a temperate climate had been unprecedented; third, infections were almost exclusively caused by clonally expanding subtypes of C. gattii, rarely reported previously; and fourth, the C. gattii infections manifested primarily as pulmonary disease, with or without meningitis. Most C. gattii patients in the Pacific Northwest (PNW) have had underlying medical conditions; approximately half had a serious underlying immune-compromising condition. HIV infection in these patients has been rare [1]. In Washington, C. gattii has been reportable as a rare disease of public health significance since 2006, and in 2011 laboratories there were required to submit to the Washington State Public Health Laboratories all Cryptococcus isolates not known to be C. neoformans; of 89 cases reported there during 2012–2013, 75 (%) have had isolates...
speciated, and of these, 30 (40%) were *neoformans*, 30 (40%) were *gattii*, and 15 (20%) were other species.

Since 2010, clinicians in 12 states (MI, MT, GA, FL, AL, SC, NC, HI, ID, AK, NM, CA) outside of the Pacific Northwest have reported at least 25 *C. gattii* infections, most in HIV-uninfected persons, to their state health departments and CDC. Many of the patients had not traveled from their home states in many years, suggesting local endemicity of *C. gattii* outside of the Pacific Northwest. Nearly all of these non-PNW-associated *C. gattii* infections have been caused by strains distinct from those associated with the PNW outbreak, and, in contrast to the primarily pulmonary disease seen with outbreak-associated *C. gattii*, non-PNW *C. gattii* patients primarily have CNS disease, with or without pulmonary involvement. Among patients with data, the one-year case-fatality rate has been ~25%. The geographic distribution of *C. gattii* infection is potentially widespread in the U.S. but remains largely unknown. Public health laboratory capacity for speciation, coupled with ongoing, systematic *C. gattii* case ascertainment and epidemiologic investigation will inform public health officials as to the incidence and distribution of infection in the United States, host and environmental risk factors, and where greater attention needs to be given to ensure that patients receive optimal care.

Because *C. gattii* is an environmental pathogen present in the air, in soil, and in water [24], it is difficult to recommend practical methods to prevent infection by it. The disease is, however, treatable with antifungal drugs. The Infectious Diseases Society of America (IDSA) provides clinical guidelines for the treatment of cryptococcal infection, including severe and non-severe pulmonary disease, and central nervous system disease [6], based almost exclusively on data from patients with *C. neoformans* infections. Recommendations include using a polyene (Amphotericin B or AmBisome®) and 5-flucytosine (5-FC) for induction treatment for severe pulmonary or central nervous system cryptococcosis; and fluconazole for treatment of mild to moderate pulmonary disease, followed by fluconazole for consolidation and maintenance therapy [6]. Lumbar puncture as needed to relieve persistently elevated intracranial pressure is also recommended. The IDSA guidelines contain only brief commentary on treatment of *C. gattii* infections, including information on the possible increased risk of cryptococcomas and a potential need for prolonged treatment.

Due to the different characteristics of *C. gattii* and *C. neoformans* infections, identification of infecting *Cryptococcus* species (*neoformans* vs. *gattii*) may be important to facilitate optimal patient treatment. However, most clinical laboratories do not identify *Cryptococcus* isolates to the species level. Automated culture machines can identify *Cryptococcus* yeasts, but, although many label the organism as “*Cryptococcus neoformans*,” they cannot distinguish *C. neoformans* from *C. gattii*. Detection of cryptococcal antigen (CrAg) in bronchoalveolar lavage or sputum, serum, or cerebrospinal fluid (CSF) is considered indicative of pulmonary infection, unspecified disseminated infection, or meningitis, respectively; however, CrAg is not species-specific. Similarly, finding cryptococcal yeast in India Ink stain of CSF does not identify the species. The simplest method for identification of cryptococcal species is culture on differential medium — usually canavanine-glycine-bromothymol blue (CGB) agar; *C. gattii* colonies turn the agar blue, while *C. neoformans* does not grow on this medium, which therefore remains greenish-yellow [7]. Culture on CGB has been used to differentiate species at CDC and in some public health and commercial reference laboratories (such as ARUP), but it is not carried by most clinical laboratories. (The process of culturing and then subculturing on CGB agar takes approximately 1 week from specimen plating. Molecular subtyping takes an additional period of time.) It is likely that many, if not most, *C. gattii* infections are missed for lack of speciation.
III. Statement of the desired action(s) to be taken

1. Utilize standard sources (e.g. reporting*) for case ascertainment for Cryptococcus gattii infection. Surveillance should employ 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 C. gattii infections.

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

2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for Cryptococcus gattii infection but do not add Cryptococcus gattii infection 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.

Other Recommendations
3. CSTE recommends that CDC perform outreach to the infectious disease community and other providers regarding the emergence and spread of C. gattii infections.
4. CSTE recommends that CDC work with public health, clinical, and reference laboratories to increase capacity to speciate Cryptococcus.

IV. Goals of Surveillance
1. To provide information on the temporal, geographic, and demographic occurrence of both outbreak-associated and sporadic C. gattii infections in the United States;
2. To facilitate optimal treatment for patients with C. gattii infection;
3. To delineate the spread of outbreak-associated C. gattii and risks to travelers; and
4. To assist with increasing health professionals’ awareness of C. gattii infection;

V. Methods for Surveillance: Surveillance for Cryptococcus gattii infection should use the recommended sources of data and the extent of coverage listed in Table III.
   - Clinician reporting
   - Laboratory reporting
   - Hospital reporting
   - Death certificates
   - Hospital discharge or outpatient records
VI. Criteria for case identification

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

Report to public health authorities any patient from whom culture of a clinical specimen has yielded *Cryptococcus gattii*; or in whom *C. gattii* infection is suspected, and from whose clinical specimen any laboratory test has indicated infection by *Cryptococcus* not proved to be *neoformans*.

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

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Clinician suspicion of <em>C. gattii</em> infection</td>
<td>N</td>
</tr>
<tr>
<td><strong>Laboratory Evidence</strong></td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>Cryptococcus gattii</em> from a clinical specimen</td>
<td>S</td>
</tr>
<tr>
<td>Detection of <em>Cryptococcus gattii</em>-specific nucleic acid in clinical specimen</td>
<td>S</td>
</tr>
<tr>
<td>Demonstration of <em>Cryptococcus gattii</em> in a clinical specimen by immunohistochemistry</td>
<td>S</td>
</tr>
<tr>
<td>Result of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), performed on a clinical specimen, specific for <em>Cryptococcus gattii</em></td>
<td>S</td>
</tr>
<tr>
<td>Isolation of <em>Cryptococcus</em> sp., not known to be <em>gattii</em>, from a clinical specimen</td>
<td>O</td>
</tr>
<tr>
<td>Detection of CrAg in serum, whole blood, urine, or CSF</td>
<td>O</td>
</tr>
<tr>
<td>Identification of <em>Cryptococcus</em> by India Ink prep of CSF</td>
<td>O</td>
</tr>
<tr>
<td>Detection of <em>Cryptococcus</em>-specific nucleic acid in a clinical specimen</td>
<td>O</td>
</tr>
<tr>
<td>Demonstration of <em>Cryptococcus</em> in a clinical specimen by histopathology or immunohistochemistry</td>
<td>O</td>
</tr>
</tbody>
</table>

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” (Optional) 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. (These optional criteria are alternatives, which means that a single column will have either no O criteria or multiple O criteria; no column should have only one O.)

C. Disease-specific data elements

*Clinical information*
- Description of clinical symptoms
- Hospitalization
• Date of onset of symptoms thought caused by cryptococcal infection
• Underlying diseases, especially HIV infection and organ transplantation

**Laboratory information**
• Date of collection of first specimen that indicated cryptococcal infection
• For specimens indicative of cryptococcal infection:
  o Specimen type
  o Specimen collection date
  o Laboratory test performed, including whether the specimen was cultured on differential CGB medium
  o Results, including cryptococcal species, if known

**Epidemiological information**
Within 2 years of symptom onset, places and dates of travel
• Outside of state
• Outside of the U.S.

VII. Case Definition for Case Classification

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

**Clinical Criteria**
• N/A

**Laboratory Criteria**
Any of the following:
• Isolation of *Cryptococcus gattii* from a clinical specimen; or
• Detection of *Cryptococcus gattii*-specific nucleic acid in clinical specimen; or
• Demonstration of *Cryptococcus gattii* in a clinical specimen by immunohistochemistry; or
• Result of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), performed on a clinical specimen, specific for *Cryptococcus gattii*.

**Epidemiologic Linkage**
N/A

Confirmed case:
A case meeting Laboratory Criteria

**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**

Cryptococcal infection is presumed to be chronic. A person may be a case only once. A new case is one that has not been previously reported.
B. Classification Tables
Table VII-B. Criteria for defining a case of cryptococcosis with *Cryptococcus gattii*.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Suspected</th>
<th>Probable</th>
<th>Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolation of <em>Cryptococcus gattii</em> from a clinical specimen</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>S</td>
</tr>
</tbody>
</table>

**Criteria to distinguish a new case:**

<table>
<thead>
<tr>
<th>Criteria to distinguish a new case:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Never reported previously</td>
<td>N</td>
</tr>
</tbody>
</table>

Notes:

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).

S = This criterion alone is Sufficient to classify a case.

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VIII. Period of Surveillance

Surveillance should be on-going.

IX. Data sharing/release and print criteria

Notification to CDC for confirmed cases of *C. gattii* infection is recommended. State-specific data will be published in the weekly MMWR and in annual summaries of notifiable diseases. Annual summaries will detail confirmed cases by state and species.

X. References

Cryptococcus gattii in British Columbia, Canada, and the Pacific Northwest of the United States.


XI. Coordination

Agencies for Response

(1) CDC
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