08-ID-09

Committee: Infectious Disease

Title: National Surveillance for Infections Caused by Free-living Amebae (*Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthamoeba* spp. (non-keratitis infections)

I. Statement of the Problem:
Infections caused by free-living amebae (*Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthamoeba* (non-keratitis infections) have been well documented worldwide. These amebae can cause fatal or severe skin and neurologic infections [e.g., *N. fowleri* causes primary amebic meningoencephalitis (PAM); several species of *Acanthamoeba* and *B. mandrillaris* cause granulomatous amebic encephalitis (GAE)]. Six fatal infections caused by *N. fowleri* in 2007 underscored that although these infections are rare, the outcomes are often severe and can undermine the public's confidence in certain public recreational activities (e.g., swimming in fresh water lakes). Making these infections nationally notifiable would likely increase the reporting of these illnesses and provide more systematic clinical, epidemiologic, and laboratory data that may assist in understanding the transmission of these amebae and increase the potential for development of future prevention recommendations.

In response to the concern over *N. fowleri* infections in 2007, CDC and CSTE formed a workgroup including state, CDC and academic partners, to review the epidemiology of reported PAM cases, review the role of environmental testing for *N. fowleri*, propose making primary amebic meningoencephalitis (PAM) and other free-living amebic infections nationally notifiable conditions, and update communication messages to educate health care providers and the public about PAM and other free-living ameba infections.

II. Background and Justification:

***Naegleria fowleri*:** Primary amebic meningoencephalitis (PAM) is a rare but nearly always fatal infection caused by *N. fowleri*, a thermophilic, free-living ameboflagellate that is ubiquitous in freshwater environments (e.g., warm bodies of freshwater such as lakes and rivers; geothermal water such as hot springs; warm water discharge from industrial plants; poorly maintained and minimally-chlorinated or unchlorinated swimming pools; and soil). PAM occurs most often in healthy children and young adults after entry of amebae-containing water into the nose during water exposure, followed by migration of amebae to the brain via the olfactory nerve. Symptoms, which occur 1–14 days after exposure, are similar to bacterial meningitis (e.g., headache, fever, stiff neck, anorexia, vomiting, altered mental status, seizures, and coma). Death typically occurs 3–7 days after the onset of symptoms.

Recent studies by the Centers for Disease Control and Prevention (CDC) have documented 121 cases in the United States dating back to 1937 from exposures in 15 southern tier states (AR, AZ, CA, FL, GA, LA, MO, MS, NC, NM, NV, OK, SC, TX, and VA), with 33 reported infections from 1998 to 2007. Most cases (85%) occurred during summer or early fall (July–September). The median age of case-patients was 12 years with a range of eight months–66 years. Males accounted for 78.2% of cases. There was only one survivor. This review found that cases that had been thought to be acquired in northern states actually had exposures in southern states. Therefore, cases that previously were thought to represent local infection from Maine, Pennsylvania, New York, and Wisconsin were reassigned to the states of exposure. Because of the extensive mobility of the U.S. population, national surveillance is important, as many cases may occur after a person who has been exposed in a southern state returns to their state of residence. PAM has been documented in most regions of the world and incidence can be expected to increase due to global climate change, population growth, and fresh water recreational exposure.

Balamuthia mandrillaris: *B. mandrillaris*, a free-living ameba that is ubiquitous in the environment, may be associated with soil or water exposure. Infection is thought to result from

either contamination of cutaneous lesions with soil or inhalation of airborne soil into the lungs or the nasal epithelium; infection is less frequently associated with stagnant water exposure. Amebae may invade the brain by a hematogenous route, most likely from a primary site of infection in the skin (e.g., ulcers or dermatitis), the respiratory tract, or via the nasal mucosa and migration along the olfactory nerve tract. Once in the brain, the amebae cause granulomatous amebic encephalitis (GAE), though the granulomatous response may be absent in immunocompromised patients. The full spectrum of disease is not yet fully understood but the acute disease is typically preceded by a sub-acute prodromal phase that may extend for as long as two years following infection with most documented infections being fatal although at least seven survivors have been documented. Signs and symptoms on initial clinical presentation often include fever, severe headache, nuchal rigidity, nausea, vomiting, hemiparesis, cranial nerve palsies, ataxia, seizures and personality change. Most *B. mandrillaris* cases occurring in the United States present with neurologic symptoms, while cases in South America, especially Peru, usually present as cutaneous lesions, described as painless skin plaques ranging in size from a few millimeters to several centimeters. After a month to 2 years, skin infections give rise to brain infections. Clinical diagnosis of *B. mandrillaris* infection is difficult because of the absence of a pathognomonic profile so initial diagnoses have suggested neurotuberculosis, acute disseminated encephalomyelitis, neurocysticercosis, viral and fungal encephalitis, or a brain tumor. The lack of recognition and subsequent delay in diagnosis may be contributing factors to its very high mortality

Early reports of *B. mandrillaris* disease in humans suggested that they occurred in very young or very old, immunocompromised patients, IV drug abusers and individuals with concurrent health problems. Recent data, however, suggest that immunocompetent individuals, especially children and adolescents, are also affected. An exhaustive review has found 50 *B. mandrillaris* case-reports from 1982-2007, with 22 reported infections from 1998 to 2007. These infections were documented in 12 states across the US (AZ, CA, CO, FL, GA, MA, MD, NC, NY, NE, OH, TX). Infections of males (59.6%) occur more often with a median age of 21 years; range 6 months to 89 years.

***Acanthamoeba* spp. (non-keratitis infections):** The genus *Acanthamoeba* includes several species of free-living amebae that often cause opportunistic infections. *Acanthamoeba* spp. are ubiquitous, occur worldwide and can be found in soil, water, and dust in the air. Amebae may invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis) or the sinuses and middle ear (from rhinitis, sinusitis, or otitis media). Once in the brain, the amebae cause granulomatous amebic encephalitis (GAE). The amebae may also invade the brain via the nasal mucosa and olfactory nerve. *Acanthamoeba* GAE has a slow and insidious onset and develops as a subacute or chronic disease lasting several weeks to months. Initial symptoms of *Acanthamoeba* GAE may include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms may include nausea, vomiting, low-grade fever, muscle aches, weight loss, mental-state abnormalities, lethargy, dizziness, loss of balance, cranial nerve palsies, other visual disturbances, hemiparesis, seizures, and coma. Once the disease progresses to the acute stage, it is generally fatal within weeks or months. However, a few documented patients have survived this infection.

Acanthamoeba GAE generally affects persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, diabetes, organ transplantation). However, a few cases have been described in individuals with no obvious signs of immunosuppression. An exhaustive review of case reports has found that from 1982-2007, 78 case-reports of *Acanthamoeba* non-keratitis infection have been documented with 18 infections reported from 1998 to 2007. These infections manifested as GAE (n=41), rhinitis (n=2), sinusitis (n=8), and cutaneous infections (n=27). The case reports are geographically diverse with reports from 22 states across the US and the District of Columbia (AL, AR, AZ, CA, CT, FL, GA, IL, KY, LA, MA, MD, MI, NE, NY, OH, OR, PA, SC, TN, TX, VA, DC). Infections of males (78.6%) predominate with a median age of 40.0 years; range 1 to 75 years.

Justification: PAM, GAE, or other types of free-living ameba infections (excluding *Acanthamoeba* keratitis infections) are not currently national notifiable diseases, and surprisingly little is known about risk factors and treatment. Making these infections nationally notifiable will

increase opportunities to identify cases, collect risk factor information, increase health care provider awareness of the disease, and obtain federal resources for research and prevention. Education of health providers and public health officials will likely improve case description information and might better describe presenting symptoms, raise awareness of the disease, and assist clinicians in differentiating free-living ameba infections from other conditions.

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

1. Add disease caused by *N. fowleri*, *B. mandrillaris*, and *Acanthamoeba* spp. (excluding keratitis) to the national notifiable disease list, and

2. Call upon CDC to work with the American Medical Association and other partners to expand physician education regarding the diagnosis and treatment of PAM, GAE, and other free-living amebic infections, and

3. Increase public education about PAM, GAE, and other free-living amebic syndromes, prevention, and early recognition.

IV. Goals of Surveillance:

Placing infections caused by free-living amebae (*N. fowleri*, *B. mandrillaris*, and *Acanthamoeba* (non-keratitis infections) under the NNDSS will help establish the burden of disease, enable improved ascertainment of risk factors, facilitate education of health care providers in the clinical presentation and diagnostic work up of suspected cases, and mobilize resources for national surveillance and public education.

V. Methods for Surveillance:

Case finding is conducted through clinician and laboratory reporting. Core surveillance data will be reported to the National Notifiable Disease Surveillance System (NNDSS) through the National Electronic Telecommunications system for Surveillance (NETSS) or the National Electronic Disease Surveillance System (NEDSS), as per state protocol.

VI. Criteria for Reporting
See Case Definitions

A. Narrative:

Reporting is to be all-inclusive and on an on-going basis.

B. Tables:

To be developed

C. Reporting disease-specific data elements:

The minimum data elements to be reported will be comprised of the core NNDSS fields. A more extensive data collection tool is under development

VII. Case Definition

<u>*Naegleria fowleri* Causing Primary Amebic Meningoencephalitis (PAM)</u>

Clinical description

N. fowleri is a free-living ameboflagellate that invades the brain and meninges via the nasal mucosa and olfactory nerve to cause acute, fulminant hemorrhagic meningoencephalitis (primary amebic meningoencephalitis – PAM), primarily in healthy children and young adults with a recent history of exposure to warm fresh water. Initial signs and symptoms of PAM begin 1 to 14 days after infection and include sudden onset of headache, fever, nausea, vomiting, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. In some cases, abnormalities in taste or

smell, nasal obstruction and nasal discharge may be seen. Other symptoms may include photophobia, mental-state abnormalities, lethargy, dizziness, loss of balance, other visual disturbances, hallucinations, delirium, seizures, and coma. After the onset of symptoms, the disease progresses rapidly and usually results in death within 3 to 7 days. Although a variety of treatments have been shown to be active against amebae in vitro and have been used to treat infected persons, most infections have still been fatal.

Laboratory-confirmed *N. fowleri* infection is defined as the detection of *N. fowleri*

1) Organisms in CSF, biopsy, or tissue specimens, or
2) Nucleic acid in CSF, biopsy, or tissue specimens.

Case classification

Confirmed: a clinically compatible illness that is laboratory confirmed. When available, molecular characterization should be reported.

Suspect: a clinically compatible illness but either further investigation is required or investigation of the case did not provide supporting evidence for the diagnosis.

Comment

N. fowleri may cause clinically-similar illness to bacterial meningitis, particularly in its early stages. Definitive diagnosis by a reference laboratory may be required.

Balamuthia mandrillaris Disease

Clinical description

B. mandrillaris is an opportunistic free-living ameba that may invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis) or the sinuses and middle ear (from rhinitis, sinusitis, or otitis media). Once in the brain, the amebae can cause a granulomatous amebic encephalitis (GAE). The amebae may also invade the brain via the nasal mucosa and olfactory nerve. *B. mandrillaris* GAE often has a slow and insidious onset and develops as a subacute or chronic disease lasting several weeks to months. *B. mandrillaris* GAE generally affects persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, IV drug use). However, cases have also occurred in young children and older adults with no obvious signs of immunosuppression. In some instances, affected individuals have had a relatively rapid clinical course. Initial symptoms of *B. mandrillaris* GAE may include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms may include nausea, vomiting, low-grade fever, muscle aches, weight loss, mental-state abnormalities, lethargy, dizziness, loss of balance, cranial nerve palsies, other visual disturbances, hemiparesis, seizures, and coma. Painless skin lesions appearing as plaques a few millimeters thick and one to several centimeters wide have been observed in some patients, especially patients outside the U.S., preceding the onset of neurological symptoms by 1 month to approximately 2 years. Once the disease progresses to the acute stage, it is generally fatal within weeks or months. However, a few patients have survived this infection.

Laboratory criteria for diagnosis

Laboratory-confirmed *B. mandrillaris* infection is defined as the detection of *B. mandrillaris*

1) Organisms in CSF, biopsy, tissue or other specimens, or
2) Nucleic acid in CSF, biopsy, tissue or other specimens.

Case classification

Confirmed: a clinically compatible illness that is laboratory confirmed. When available, molecular characterization should be reported.

Probable: a clinically compatible illness with serologic evidence of infection (≥1:128) but lacking appropriate tissue specimens for further confirmatory testing.

Comment

B. mandrillaris and *Acanthamoeba spp.* may cause clinically-similar illnesses and may be difficult to differentiate using commonly-available laboratory procedures. Definitive diagnosis by a reference laboratory may be required. A negative test on CSF does not rule out infection because the organism load in the CSF is often low.

Acanthamoeba Disease (excluding keratitis)

Clinical description

The genus *Acanthamoeba* includes several species of opportunistic free-living amebae that may invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis) or the sinuses and middle ear (from rhinitis, sinusitis, or otitis media). Once in the brain, the amebae cause a granulomatous amebic encephalitis (GAE). The amebae may also invade the brain via the nasal mucosa and olfactory nerve. *Acanthamoeba* GAE has a slow and insidious onset and develops as a subacute or chronic disease lasting several weeks to months. *Acanthamoeba* GAE generally affects persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, diabetes, organ transplantation). However, a few cases have been described in individuals with no obvious signs of immunosuppression. Initial symptoms of *Acanthamoeba* GAE may include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms may include nausea, vomiting, low-grade fever, muscle aches, weight loss, mental-state abnormalities, lethargy, dizziness, loss of balance, cranial nerve palsies, other visual disturbances, hemiparesis, seizures, and coma. Once the disease progresses to the acute stage, it is generally fatal within weeks or months. However, a few patients have survived this infection.

Laboratory-confirmed *Acanthamoeba* spp. infections (excluding keratitis) are defined as the detection of *Acanthamoeba* spp.

1) Organisms in CSF, biopsy, tissue or other specimens, or
2) Nucleic acid in CSF, biopsy, tissue or other specimens.

Case classification

Confirmed: a clinically compatible illness that is laboratory confirmed. When available, species designation and molecular characterization should be reported.

Suspect: a clinically compatible illness but either further investigation is required or investigation of the case did not provide supporting evidence for the diagnosis.

Comment

Acanthamoeba and *B. mandrillaris* may cause clinically-similar illnesses and may be difficult to differentiate using commonly-available laboratory procedures. Definitive diagnosis by a reference laboratory may be required. Several species of Acanthamoeba are associated with infection (i.e., *A. castellanii, A. culbertsoni, A. hatchetti, A. healyi, A. polyphaga, A. rhysodes, A. astonyxis, A. lenticulata and A. divionensis*).

B. Classification Tables:

	Clinicians	Laboratories
Confirmed	Report all cases of that meet the confirmed case definition – those having a positive laboratory test.	Report all cases that meet the laboratory criteria for reporting.
Suspected	Report all cases meeting the clinical presentation that they consider to be a suspect case	

VIII. Period of Surveillance:
Reporting is to be on-going. The surveillance case definition will be effective January 1, 2009.

IX. Data sharing/release and Print criteria:
States and territories will send both core/generic and supplemental/extended data to CDC. Only fully de- identified case data will be released to the general public. Final printed counts published in MMWR by CDC will distinguish between confirmed and suspected cases. Provisional case report data will not be used until verification procedures are completed.

X. References:
NA

XI. Coordination:

Agencies for Response:

(1) Julie L. Gerberding, MD
Director
Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333
404-639-7000
jyg2@cdc.gov

(2) Michael J. Beach, PhD Associate Director
National Center for Zoonotic, Vector-Borne and Enteric Diseases (NCZVED)
Atlanta, GA 30333
770-488-7763
MBeach@cdc.gov

XII. Submitting Author:

(1) John P. Middaugh
State Epidemiologist
Florida Department of Health
4052 Bald Cypress Way
Bin #A07
Tallahassee, FL 32399-1708
City, State and Zip
850-245-4356
john_middaugh@doh.state.fl.us

Table 1. Common core data elements for case reporting to a public health agency from a healthcare provider: To be included in the initial case report.

	Non Condition Specific Data Elements	***Core Data Set***
Reporting Information		
	Date of report	X
	Reporter name	X
Reporter Contact Information		
	Telephone	X
	Address	X
Health Care Provider Information		
	Health care provider name	X
	Facility Name	X
Facility/Provider Contact Information		
	Phone number	X
	Address	X
Subject Information		
	First Name	X
	Middle Name	X
	Last Name	X
	Street	X
	City	X
	State	X
	ZIP	X
	Telephone	X
	Age	X
	Date of birth	X
	Gender	X
Clinical Information		
	Name of Condition	X
	Date of onset	X