

Amebic Meningitis/Encephalitis rev Jan 2018

BASIC EPIDEMIOLOGY

Infectious Agent

Naegleria fowleri, *Acanthamoeba* spp. and *Balamuthia mandrillaris* are microscopic, free-living amoebae (single-celled living organisms). *Naegleria fowleri* is the causal agent of primary amebic meningoencephalitis (PAM), while *Acanthamoeba* spp. and *Balamuthia mandrillaris* are the causal agents of granulomatous amebic encephalitis (GAE).

- *Naegleria fowleri* is a heat-loving (thermophilic), free-living amoeba (single-celled microbe) commonly found around the world in warm fresh water (e.g., lakes, rivers, hot springs) and soil. *N. fowleri* is the only species of *Naegleria* known to infect people. Most of the time, the amoeba lives in freshwater habitats by feeding on bacteria. However, in rare instances, the amoeba can infect humans by entering the nose during water-related activities.
- *Acanthamoeba* species are found worldwide. Most commonly the amoebae are found in soil, dust, fresh water, brackish water (e.g., a marsh) and sea water. *Acanthamoeba* spp. can also be found in swimming pools, hot tubs and drinking water systems (e.g., slime layers in pipes and taps), as well as in heating, ventilating and air conditioning (HVAC) systems and humidifiers. Several species of *Acanthamoeba*, including *A. culbertsoni*, *A. polyphaga*, *A. castellanii*, *A. astronyxis*, *A. hatchetti*, *A. rhysodes*, *A. divionensis*, *A. lugdunensis* and *A. lenticulata* are implicated in human disease.
- *Balamuthia mandrillaris* is found in soil and believed to enter the body through skin wounds and cuts, or when dust containing *Balamuthia mandrillaris* is breathed in or gets in the mouth. Exposure to *Balamuthia mandrillaris* is likely to be common because of how widespread the amoeba is in the environment. However, very few cases of disease in humans have been found worldwide since *Balamuthia mandrillaris* was discovered.

Transmission

Naegleria fowleri

Transmission of *N. fowleri* to humans occurs when water containing the amoeba enters the body through the nose. Trophozoites infect humans or animals by penetrating the nasal tissue and migrating to the brain via the olfactory nerves causing primary amebic meningoencephalitis. Exposure occurs when people go swimming or diving in warm freshwater places, like lakes and rivers. People do not become infected by drinking contaminated water. In very rare instances, *Naegleria* infections may also occur when contaminated water from other sources (e.g., inadequately chlorinated swimming pool water or contaminated tap water) enters the nose. Some examples are when people submerge their heads or cleanse during religious practices, and when people irrigate their sinuses (nose) using contaminated tap water. It is also possible that *Naegleria* infection could be acquired through transplantation of organs from an infected donor.

Acanthamoeba spp.

Acanthamoeba spp. can enter the body through the eye, the nasal passages, cuts or skin wounds or by being inhaled into the lungs. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body through various means. When *Acanthamoeba* spp. enter the eye they can cause severe keratitis in otherwise healthy individuals, particularly contact lens users. When the amoeba enters the respiratory system or through the skin, it can invade the central nervous system by hematogenous dissemination causing granulomatous amebic encephalitis (GAE) or disseminated disease, or skin lesions in individuals with compromised immune systems.

Balamuthia mandrillaris

Balamuthia mandrillaris GAE occurs when the amebae infect the body, possibly through skin wounds and cuts, or when dust containing *Balamuthia* is breathed in through the nose or mouth. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body through various means. Entry can occur through the nasal passages to the lower respiratory tract, or through ulcerated or broken skin. When *B. mandrillaris* enters the respiratory system or through the skin, it can invade the central nervous system by hematogenous dissemination causing granulomatous amebic encephalitis (GAE) or disseminated disease. The ameba can also cause skin lesions in individuals who are immune competent as well as those with compromised immune systems. *Balamuthia mandrillaris* infection also may be acquired through transplantation of infected donor organs.

Incubation Period and Illness Duration*Naegleria fowleri*:

- Incubation period: Symptoms start 1-9 days (median 5 days) after exposure
- Duration of illness: Death occurs 1-18 days (median 5 days) after symptoms begin

Balamuthia mandrillaris and *Acanthamoeba* spp.:

- Incubation period: Weeks to months (or longer)
- Duration of illness: Weeks to months

Communicability

Amebic meningitis/encephalitis is not spread person-to-person (except in the case of transmission through transplantation of organs from an infected donor).

Clinical Illness*Primary amebic meningoencephalitis (PAM)*

Infections with *Naegleria fowleri* cause the rare disease PAM, a brain infection that leads to the destruction of brain tissue. Infection can occur in young immune-competent individuals. In its early stages, the infection may be similar to bacterial meningitis. Initial symptoms of PAM start 1 to 9 days after infection. Initial symptoms may include headache, fever, nausea, or vomiting. Later symptoms may include stiff neck, confusion, lack of attention to people and surroundings, a loss of balance, seizures and hallucinations. These symptoms are followed by coma and death. After the start of symptoms, the disease progresses rapidly and death occurs within 18 days, usually on the fifth or sixth day.

Granulomatous amebic encephalitis (GAE)

GAE - caused by *Balamuthia mandrillaris* and *Acanthamoeba* species - often has a slow, insidious onset and then develops into a subacute or chronic disease lasting several weeks to months. However, *B. mandrillaris* infections associated with organ transplantation have an especially rapid clinical course.

GAE caused by *Acanthamoeba* spp. can cause a serious infection of the brain and spinal cord. Symptoms may include headaches, stiff neck, nausea and vomiting, tiredness, confusion, lack of attention to people and surroundings, loss of balance and bodily control, seizures and hallucinations. Symptoms progress over several weeks and death usually occurs. Skin infections do not necessarily lead to disseminated disease.

GAE and disseminated infection are very rare forms of *Acanthamoeba* spp. infection and primarily affect people with compromised immune systems. While unusual, disseminated infection can also affect healthy children and adults. Conditions that may increase a patient's risk for GAE and disseminated infection include AIDS, organ/tissue transplant, steroids or excessive use of antibiotics, diabetes mellitus, cancer, disorders in which white blood cells in the lymphatic tissue are over-produced or abnormal, disorders in which blood cells or blood clotting mechanisms do not function properly or are abnormal, liver cirrhosis and lupus.

Balamuthia mandrillaris infection can cause a wide range of symptoms. Disease can begin with a skin wound on the face, trunk or limbs and can then progress to the brain where it causes GAE. Diagnosis of *Balamuthia mandrillaris* GAE can be difficult, but some early symptoms may include headaches, stiff neck or head and neck pain with neck movement, sensitivity to light, nausea, vomiting, lethargy and low-grade fever. Other signs of *Balamuthia mandrillaris* GAE may include behavioral changes, seizures, weight loss, partial paralysis, speech difficulties and difficulty walking. *Balamuthia* can also cause a widespread infection involving multiple body parts. The disease might appear mild at first but can become more severe over weeks to several months. *Balamuthia mandrillaris* GAE is a very rare but usually fatal disease. Overall, the outlook for people with this disease is poor, although early diagnosis and treatment may increase the chances for survival.

Balamuthia mandrillaris is able to infect anyone, including healthy people. Those at increased risk for infection include people with HIV/AIDS, cancer, liver disease or diabetes mellitus; people taking immune system inhibiting drugs; alcoholics; young children or the elderly and pregnant women.

Severity

PAM and GAE cases are often fatal. The fatality rate for PAM is over 97%. Only 4 people out of 143 known infected individuals in the United States from 1962 to 2016 have survived. The death rate for *Balamuthia mandrillaris* GAE is more than 89% and the death rate for *Acanthamoeba* GAE is more than 90%.

DEFINITIONS

Amebic meningitis/encephalitis is classified as either primary amebic meningoencephalitis (if it is caused by *Naegleria fowleri*) or as Other Amebic Meningitis/Encephalitis (if it is caused by another ameba). See the case definitions for both conditions below.

Clinical Case Definition of PAM

An infection presenting as meningoencephalitis or encephalitis. The clinical presentation of PAM is like that of acute meningitis caused by other pathogens and symptoms include headache, nausea, vomiting, anorexia, fever, lethargy, and stiff neck. Disorientation, mental status changes, seizure activity, loss of consciousness, and ataxia may occur within hours of initial presentation. After the onset of symptoms, the disease progresses rapidly and usually results in death within 3 to 7 days.

Laboratory Confirmation of PAM

Detection of *Naegleria fowleri* from a clinical specimen via:

- Detection of nucleic acid (e.g., PCR), **OR**
- Detection of antigen (e.g., immunohistochemistry)

Note: When available, molecular characterization (e.g., genotype) should be reported.

Comments: *Naegleria fowleri* might cause clinically similar illness to bacterial meningitis, particularly in its early stages. Definitive diagnosis by a reference laboratory is required. Unlike *Balamuthia mandrillaris* and *Acanthamoeba* spp., *N. fowleri* is commonly found in the CSF of patients with PAM.

Case Classifications for PAM

- **Confirmed:** A clinically compatible case that is laboratory confirmed
- **Probable:** A clinically compatible case that meets at least one of the supportive laboratory criteria (listed below) and does not meet confirmatory lab criteria
 - Supportive laboratory evidence:
 - Visualization of motile amebae in a wet mount of CSF
 - Isolation of *N. fowleri* in culture from a clinical specimen

Clinical Case Definition of Other Amebic Meningitis/Encephalitis

An infection presenting as meningoencephalitis or encephalitis. Granulomatous amebic encephalitis (GAE) can include general symptoms and signs of encephalitis such as early personality and behavioral changes, depressed mental status, fever, photophobia, seizures, nonspecific cranial nerve dysfunction, and visual loss. GAE neurologic infections are generally fatal within weeks or months; however, a few patients have survived.

Laboratory Confirmation of Other Amebic Meningitis/Encephalitis

Detection of *Acanthamoeba*, *Balamuthia*, or another non-*Naegleria* free-living amoeba from a clinical specimen or culture via:

- Detection of nucleic acid (e.g., PCR), **OR**
- Detection of antigen (e.g., immunohistochemistry)

Comments: *Acanthamoeba* spp. and *B. mandrillaris* can cause clinically similar illnesses and might be difficult to differentiate using commonly available laboratory procedures. Definitive diagnosis by a reference laboratory might be required. A negative test on CSF does not rule out *Acanthamoeba* spp. or *B. mandrillaris* infection because these organisms are not commonly present in the CSF.

Case Classifications for Other Amebic Meningitis/Encephalitis

- **Confirmed:** A clinically compatible case that is laboratory confirmed
- **Probable:** No probable case definition

Note: *Acanthamoeba* species and *Balamuthia mandrillaris* can also cause disseminated disease (affecting multiple organ systems) or cutaneous disease. For *B. mandrillaris* disease, 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 neurologic symptoms by 1 month to approximately 2 years. Skin lesions and sinus disease may be seen in *Acanthamoeba* disease. Disseminated disease and cutaneous disease caused by free-living amoebae are only voluntarily reportable in Texas unless they progress to meningitis or encephalitis.

Cluster and Outbreak Definitions for PAM and Other Amebic Meningitis/Encephalitis

- Cluster:
 - Two or more cases linked by place of residence or places visited within 1 year
- Outbreak:
 - Two or more cases associated with the same body of water or other common water exposure event/practice (e.g., Neti pot usage for nasal irrigation) within 1 year

SURVEILLANCE AND CASE INVESTIGATION**Case Investigation**

Local and regional health departments should investigate all reports of suspected amebic meningitis or encephalitis. Primary amebic meningoencephalitis cases tend to receive substantial amounts of attention from the community and the media.

Case Investigation Checklist

- Confirm that laboratory results meet the case definition.
- Arrange for specimens to be sent to the Centers for Disease Control and Prevention (CDC) (if specimens have not already been sent).
- Review medical records or speak to an infection preventionist or physician to verify that the case meets case definition, and to obtain information on underlying health conditions and course of illness.

- Interview the case (or surrogate) to identify risk factors.
 - If multiple attempts were made to contact the case or surrogate and attempts were unsuccessful, please fill out the case investigation form with as much information as possible and indicate the reason for missing information (e.g., lost to follow-up - patient did not return call; multiple messages left).
- Ensure that appropriate control measures are implemented (see Control Measures section, below).
- Complete the Free Living Ameba Case Report form (available at <http://www.dshs.texas.gov/idcu/investigation>) and fax or secure email it to DSHS.
- Enter and submit for notification in the NEDSS Base System (NBS) all confirmed and probable case investigations.

Control Measures

Naegleria fowleri

- Provide education on primary amebic meningoencephalitis (PAM) as needed with emphasis on the rarity of disease.
 - Although infections are severe, the risk of *Naegleria fowleri* infection is very low. There have been 30 reported infections in the U.S. during the 10 years from 2000–2009, despite millions of recreational water exposures each year. By comparison, during the 10 years from 1996–2005, there were over 36,000 drowning deaths in the U.S.
 - It is likely that a low risk of *Naegleria fowleri* infection will always exist with recreational use of warm freshwater lakes, rivers and hot springs. The low number of infections makes it difficult to know why some people have been infected compared to the millions of other people using the same or similar waters across the U.S.
 - The only way to prevent *Naegleria fowleri* infections is to refrain from water-related activities. For individuals who plan to take part in water-related activities, provide education on risk reduction (see below).
- Provide education on prevention of exposure.
 - <http://www.cdc.gov/parasites/naegleria/prevention.html>
 - Avoid water-related activities in warm freshwater during periods of high water temperature.
 - Hold the nose shut, use nose clips, or keep your head above water when taking part in water-related activities in bodies of warm freshwater such as lakes, rivers or hot springs.
 - Avoid digging in, or stirring up, the sediment while taking part in water-related activities in shallow, warm freshwater areas.
 - *Naegleria fowleri* infections have been reported when people put their heads underwater, rinse their sinuses through the nose, and cleanse their noses during religious practices (e.g., ritual nasal rinsing and ablution) using contaminated tap or faucet water. If you perform nasal irrigation or sinus flushes (e.g., using a Neti pot) for any reason, be sure to use only sterile, distilled or lukewarm previously boiled water.
- Recommend that anyone experiencing symptoms be evaluated by a physician.
- Posting of signs mentioning the presence of *Naegleria fowleri* in bodies of water is not generally recommended since the *N. fowleri* ameba is ubiquitous in nature. There are no guidelines or supporting evidence for the posting or removal of such signs. Posting of safe swimming practices might be a preferred alternative.
- Several drugs are effective against *Naegleria fowleri* in the laboratory. However, their effectiveness in humans is unclear since almost all infections have been fatal even when people were treated. See the CDC's Primary Amebic Meningoencephalitis (PAM) treatment website for more information on available treatments for patients with free-living ameba infections at <http://www.cdc.gov/parasites/naegleria/treatment-hcp.html>.

Balamuthia mandrillaris and *Acanthamoeba* spp.

- There are no specific prevention and control measures for *B.mandrillaris* and *Acanthamoeba* spp.
- Provide education on Granulomatous Amebic Encephalitis as needed with emphasis on the rarity of disease.
- Recommend that anyone experiencing symptoms be evaluated by a physician.
- Although infections are severe, the risk of *B.mandrillaris* and *Acanthamoeba* spp. infection is very low. It mainly affects those who are immunocompromised.

School/Daycare Exclusion Criteria

No exclusion is required for disease control purposes.

MANAGING SPECIAL SITUATIONS

Multiple Cases Associated with a Single Water Source

If one or more cases occur that are associated with a single water source within a one-year period, notify the DSHS EAIDU at (800) 252-8239 or (512) 776-7676.

REPORTING AND DATA ENTRY REQUIREMENTS

Provider, School, Child-Care Facility, and General Public Reporting Requirements

Confirmed, probable, and clinically suspected cases are required to be reported **within 1 week** to the local or regional health department or to DSHS EAIDU at (800) 252-8239 or (512) 776-7676.

Local and Regional Reporting and Follow-up Responsibilities

Local and regional health departments should:

- Enter the case into NBS and submit an NBS notification on all **confirmed and probable** cases to DSHS within 30 days of receiving a report of a confirmed or probable case.
 - Please refer to the *NBS Data Entry Guidelines* for disease-specific entry rules.
 - A notification can be sent as soon as the case criteria have been met. Additional information from the investigation may be entered upon completion of the investigation.
- Fax, securely email, or mail a completed investigation form when the NBS notification is submitted.
 - Investigation forms may be faxed to **512-776-7616**, securely emailed to the IRID Epidemiologist I or IRID team lead, or mailed to:
 - Infectious Disease Control Unit
 - Texas Department of State Health Services
 - Mail Code: 1960
 - PO Box 149347
 - Austin, TX 78714-9347

When an outbreak is investigated, local and regional health departments should:

- Report outbreaks within 24 hours of identification to the regional DSHS office or to EAIDU at **512-776-7676**.
- For waterborne outbreaks, submit a completed **National Outbreak Reporting System (NORS)** outbreak form at the conclusion of the outbreak investigation.
 - Enter into NORS online reporting system at <https://wwwn.cdc.gov/nors/login.aspx>
 - Forms, training materials, and other resources are available at <http://www.cdc.gov/nors/>
- To request a NORS account, please email FoodborneTexas@dshs.texas.gov
 - Please put in Subject Line: NORS User Account Request
 - Information needed from requestor: name, email address, and agency name
 - After an account has been created a reply email will be sent with a username, password, and instructions for logging in.

LABORATORY PROCEDURES

It is recommended that CSF, serum and tissue specimens (including biopsy, surgical or necropsy specimens) be collected for the detection of free-living amoebae (*Naegleria fowleri*, *Balamuthia mandrillaris* and *Acanthamoeba* spp.) and sent directly to the CDC along with the CDC Form for Free-living Amoebae (FLA) Testing (request by emailing dpdx@cdc.gov) and the CDC 50.34 Submission Form (available at <http://www.cdc.gov/laboratory/specimen-submission/index.html>).

Clinicians who suspect amebic meningitis/encephalitis (including PAM) should contact their state health department and/or CDC (24/7 Emergency Operation Center - 770-488-1700). CDC can assist with diagnosis and provide treatment recommendations. Telediagnosis can be arranged at CDC by emailing photos through DPDx, CDC's Division of Parasitic Diseases and Malaria telediagnosis tool. Instructions for submitting photos through DPDx are available at the [DPDx Contact Us page](#).

Important note: For CSF samples - Do NOT refrigerate or freeze; Do NOT centrifuge (Refrigeration or freezing will rapidly lyse and kill the amoebae, preventing visual detection and identification.)

- The DSHS Parasitology Laboratory may be contacted for assistance and coordination in submitting specimen samples and electronic images to the CDC. The team lead, Cathy Snider, will work with the hospital to coordinate all CSF specimen shipments to the CDC.

Cathy Snider – Team leader – Parasitology

DSHS Parasitology Lab

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Email: cathy.snider@dshs.texas.gov

Specimen Collection

The following CDC guidelines are available at <http://www.cdc.gov/parasites/naegleria/diagnosis-hcp.html>.

Tissue specimens - including biopsy, surgical or necropsy specimens - may be collected for the detection of free-living amoebae (*Naegleria*, *Balamuthia* and *Acanthamoeba*).

A. Specimens Needed for Pre-Mortem Diagnosis

Clinical Pre-Mortem Specimens for Diagnosis at CDC:

If possible, CDC requests that the following specimens be sent for diagnostic testing at CDC:

- Fresh CSF (Please DO NOT FREEZE and DO NOT REFRIGERATE as this kills the amoebae)
- If the patient has had a biopsy, the following are also requested:
 - Fresh brain tissue (Please DO NOT FREEZE and DO NOT REFRIGERATE)
 - Formalin-fixed and paraffin embedded tissues
 - Three stained hematoxylin and eosin (H&E) slides

B. Specimens Needed for Post-Mortem and Autopsy Diagnosis

To better understand the pathogenesis of PAM and the potential for transmission via organ transplantation, CDC would like to encourage autopsies for PAM case patients whose families consent.

- CNS Tissue: *Naegleria fowleri* is most likely detected in biopsy or autopsy tissue collected from the area surrounding the nasal-olfactory bulbs in the brain. However, CDC requests that tissues be collected from other CNS sites in addition to the olfactory bulb to look for other possible locations of ameba entry into the brain, such as around the auditory nerve.
- Extra-CNS Tissue: All possible steps should be taken to minimize the possibility of cross-tissue contamination between CNS and extra-CNS tissues. These steps should, at a minimum, include:
 - Completing the gross examination and sample collection from all extra-CNS tissues prior to examination of the CNS tissues
 - Utilizing separate workspaces and dissecting tools for the extra-CNS and CNS tissues
 - Placing recovered samples of extra-CNS and CNS tissues in separate formalin containers
 - Processing all tissues, particularly extra-CNS and CNS, separately
 - Cutting extra-CNS and CNS tissues separately
 - If the same equipment is used to cut the tissue, cut extra-CNS tissues first and include a cleaning step in between different tissues.

Specimens can then be sent to CDC.

Clinical Specimens for Diagnosis at CDC

If possible, please send the following specimens:

- Fresh CSF (Please DO NOT FREEZE and DO NOT REFRIGERATE as this kills the amebae)
- Fresh, unfixed brain tissue
- Fresh, unfixed tissue (other than brain)
- Formalin-fixed, paraffin-embedded, tissue
 - Three H&E-stained slides
 - Six unstained slides (for indirect immunofluorescence, or IIF)
 - Paraffin-embedded tissue block
- Photos of gross brain morphology
 - Particularly around olfactory and auditory areas
- Serum

Submission Forms

- The FLA specimen submission form for free-living amebae (FLA) testing can be requested by emailing dpdx@cdc.gov. In addition, the CDC 50.34 Specimen Submission Form (available at <http://www.cdc.gov/laboratory/specimen-submission/form.html>) is also required for FLA testing.

Specimen Shipping

- Ship samples according to shipping guidelines and requirements available at <http://www.cdc.gov/dpdx/diagnosticProcedures/other/FLA.html> and <http://www.cdc.gov/dpdx/diagnosticProcedures/other/shipment.html>.
- Unfixed specimens for culture should be sent at ambient temperature by overnight priority mail. For PCR, sterile unfixed specimens or specimens in 70-90% ethanol should be sent by overnight priority mail on ice packs. Care should be taken to pack glass slides securely, as they can be damaged in shipment if not packed in a crush-proof container.

- **Please ship Monday through Thursday, overnight.** Packages cannot be accepted on weekends or federal holidays. Please send any fresh tissue, CSF, whole blood or serum specimens by overnight express:

CDC
SMB/STAT Lab
Attn: Unit 53
1600 Clifton Road, NE
Atlanta, GA 30333
Ph: 404-718-4157; 404-718-4878

- For additional information about tissue specimens or shipping, please contact the CDC Division of Parasitic Diseases at dpdx@cdc.gov or 404-718-4110.

Digital Laboratory and Pathology Image Submission

- Please send your diagnostic request to dpdx@cdc.gov. When submitting your request, please include the following information along with your message:
 - Your name
 - Your affiliation
 - Your telephone contact number (optional)
- **PLEASE NOTE:** Effective immediately, the CDC's DPDx Team will require a [CDC 50.34 submission form](#) to be filled out and submitted with images for diagnostic assistance in order to generate a formal, written laboratory report. This form must be submitted in a secure method to protect patient information. The CDC has a Sharefile system that should be used to submit the form and images. Please email the DPDx Team to request a one-time link to the Sharefile server to submit a case for diagnostic assistance. The Team will include a CDC CSID number for the case in the subject line when they email the link and that number will be used for any subsequent correspondence (when necessary). The following steps describe the submission process:
 - Send an email requesting diagnostic assistance to dpdx@cdc.gov. DO NOT include patient identifiers or images in the email requesting diagnostic assistance.
 - The DPDx team will respond by email with a CDC Sharefile link, open this link in your browser.
 - Upload your case images and [CDC 50.34 submission form](#). Other supporting documents and communications such as questions, etc. can also be uploaded as word or text files.
 - The DPDx team will receive notification once the files are uploaded and will respond via email with a preliminary diagnosis using the CDC CSID number assigned.
 - An official, final diagnosis will be generated only if the CDC 50.34 is submitted.

UPDATES

January 2018

- Basic Epidemiology: updated the fatality rates for PAM and GAE
- Surveillance and Case Investigation: updated web addresses/links
- Reporting and Data Entry Requirements: added that completed case investigation forms may be sent to the IRID Epidemiologist I or IRID team lead by secure email
- Laboratory Procedures: updated "Specimens Needed for Pre-Mortem Diagnosis" information and updated the process for requesting diagnostic assistance from the CDC DPDx Team