16-ID-12

Committee: Infectious Disease

Title: Public Health Reporting and Standardized Surveillance for Free-living Amebae Infections including *Acanthamoeba* Disease, *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* Causing Primary Amebic Meningoencephalitis

I. Statement of the Problem

The epidemiology of disease caused by *Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthamoeba* species has evolved in recent years to include risk factors other than warm recreational freshwater exposure in southern tier states and soil exposure. Recent developments include expansion of the geographic range of *N. fowleri* infection to northern and Midwestern states, the identification of nasal irrigation for either medical or religious purposes as a risk factor for infection, and the finding of *N. fowleri* in a treated public drinking water distribution system. Solid organ transplantation has also recently emerged as a risk factor for *Balamuthia mandrillaris* infection in organ recipients. The purpose of this position statement is to update the existing standardized case definitions for each condition to reflect changes in testing and diagnostic capabilities.

II. Background and Justification

Background

Free-living amebae (FLA) infections include the conditions of primary amebic meningoencephalitis (PAM), caused by infection with *N. fowleri*, and granulomatous amebic encephalitis (GAE), disseminated, and cutaneous infections caused by infection with *B. mandrillaris* and *Acanthamoeba* spp. *N. fowleri*, *B. mandrillaris*, and *Acanthamoeba* spp. are amebae that live freely in the environment without the need for a host. These FLA generally complete their entire life cycles in the environment, such as in fresh water and soil, and were initially considered to be harmless environmental organisms. However, FLA are now known to be capable of endozoic living (within a mammal) and therefore, on rare occasions and for reasons not well understood, can infect and sicken humans who have been exposed. Although human infections are thought to be rare, the true numbers are unknown. Since these amebae are often not suspected as the cause of illness, diagnostic testing is not available in clinical or state public health laboratories, and these conditions are not reportable in most states.

N. fowleri is found in warm freshwater, bottom sediment and soil, and proliferates during warm weather. *N. fowleri* can infect humans, causing an acute, central nervous system infection (PAM) that is usually fatal. *N. fowleri* infections are acute – the mean time from symptom onset to death is 5 days. The parasite enters humans via the intact or disrupted nasal mucosa, crosses the cribriform plate, migrates along the basilar brain from the olfactory bulbs and tracts to the cerebellum, deeply penetrates the cortex to the periventricular system, and incites a purulent meningoencephalitis with rapid cerebral edema, resulting in early fatal brain herniation.

There have been 138 reported PAM cases from 1962–2015 in the United States, with three known survivors (1–4). Historically, those at highest risk are young immunocompetent males who participate in water sports during the summer in southern tier states. However, in the last five years, two cases were reported from Minnesota (2010 and 2012), as well as two cases from Kansas (2011 and 2013), and one case from Indiana (2012), leading to some concern that the range of *N. fowleri* infections may be expanding (5). Additionally, prior to 2011, Virginia had not reported a case since 1969. In 2011, two cases of PAM were identified in Louisiana; the case-patients did not have recreational water exposure, but did perform nasal and sinus irrigation with a neti pot using a salt solution reconstituted with *N. fowleri*-contaminated tap water (6). *N. fowleri* was subsequently shown to have colonized the residential plumbing system (water heater) of the implicated home similar to other premise plumbing biofilm pathogens like

Legionella, *Pseudomonas*, and nontuberculous mycobacteria (7). Additionally, in 2012, a case of PAM was reported from St. Thomas, U.S. Virgin Islands in which the case-patient did not have recreational freshwater exposure but was known to practice nasal rinsing for religious purposes using residential plumbing tap water (8). In 2013, a case of PAM was reported from Louisiana in a 4-year-old who did not have exposure to untreated recreational water but was exposed to tap water used to supply a backyard water slide. A subsequent environmental investigation demonstrated *N. fowleri* in water samples taken from the disinfected public drinking water distribution system (9).

B. mandrillaris is found worldwide in freshwater and soil year-round and causes GAE. It can also affect other organs including skin, lung, adrenal glands, kidney and pancreas. The mean time from symptom onset to death for *B. mandrillaris* infection is 74 days. Of 94 reported U.S. cases from 1974–2014, there have been 10 known survivors (survival rate 11%) (10). The median age of *B. mandrillaris* patients was 33 years and 67% were male. The exposure source to *B. mandrillaris* for all reported cases was unknown, but thought to be soil or water. The exact incubation period is also unknown, since the timing and type of exposure is unknown. In the recent *B. mandrillaris* organ transplant clusters where the timing of exposure was known, the incubation periods ranged from 18–25 days. Cases have been located across the U.S. and there is no apparent seasonality to infections. Patients with *B. mandrillaris* infection are sometimes immunosuppressed. Recently, three clusters of transplant-associated *B. mandrillaris* GAE have been identified where *B. mandrillaris* infection was confirmed in the organ donors after it was initially diagnosed in organ recipients: Mississippi in 2009, Arizona in 2010, and Alabama in 2012, (11, 12).

Acanthamoeba spp. are thought to be ubiquitous in the environment, and like *B. mandrillaris*, cause GAE as well as disseminated infections. Of 118 reported U.S. cases from 1955–2012, there have been 11 known survivors (survival rate 9%). There are no known U.S. survivors of *Acanthamoeba* spp. GAE; all survivors had cutaneous, sinus, or disseminated disease not involving the brain. The mean age of *Acanthamoeba*-infected patients was 39 years, and 73% were male (CDC unpublished data). Patients were frequently immunosuppressed. Cases have been identified across the U.S. and there is no apparent seasonality.

Based on what is known about the clinical presentation and epidemiologic features of these FLA infections and their high mortality rates, clinicians and public health authorities should have a high level of suspicion for these infections when certain elements are present in the patient's history and presentation. Patients presenting with meningoencephalitis or encephalitis who

- have a history of swimming in warm freshwater in the two weeks prior to their illness onset or
- have performed nasal or sinus irrigation in the two weeks prior to their illness onset and
- have no other explanation for their illness

should be investigated as a possible PAM case. Initial investigations by the clinician should include a CSF wet mount to look for motile amebae and alerting public health authorities to facilitate expert recommendations for confirmatory diagnosis and treatment.

Similarly, clinicians caring for patients presenting with encephalitis with a history of solid organ transplant who, after more routine causes of encephalitis have been investigated and ruled out, should consider the diagnosis of *B. mandrillaris* or *Acanthamoeba* spp. GAE.

Justification

CSTE position statement 11-ID-15 established a standard set of case definitions for four separate FLA infections (*Acanthamoeba* Disease (excluding keratitis), *Acanthamoeba* Keratitis, *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM)) needed for supporting voluntary nationwide surveillance for these infections. Culture of ameba does not specifically identify species or genera, as is found with selective culture of bacteria. Therefore, extensive morphological expertise, which is rarely available in clinical laboratories, is required to identify ameba from culture. Additionally, with the increased use of advanced molecular diagnostics for FLA infection

diagnostic testing and less reliance on visualization alone to identify amebae, the standard case definitions for FLA infections should also be revised to reflect these changes in testing practices.

Currently, amebic meningoencephalitis/encephalitis or FLA infection is a reportable condition in three states that historically have borne the burden of *N. fowleri* PAM cases: Florida, Texas, and Louisiana. However, with the identification of *N. fowleri* cases in northern and Midwestern states and *B. mandrillaris* transplant clusters that involved multiple state and local jurisdictions, the documented occurrence of disease has moved beyond the southern-tier states and has become a condition of national concern. It is not known if *N. fowleri* or *Acanthamoeba* spp. can also be transmitted through solid organ transplantation; therefore, ongoing national surveillance for these infections is imperative to identify potential new modes of transmission.

Since 2013, CDC has provided the investigational drug miltefosine for patients with suspected FLA infections. To meet the requirements of the investigational new drug protocol, clinicians using miltefosine to treat an FLA patient were required to complete a case report form. Now that miltefosine is commercially available, CDC will no longer be the only source for this drug and will lose this mechanism for collecting surveillance data.

Additionally, national surveillance for FLA infections will allow for the identification of transmission routes and risk factors that will inform the development of prevention messages. Though these infections remain rare, their severe outcomes can undermine the public's confidence in their drinking water supply, in recreational activities such as swimming, and in medical procedures like solid organ transplantation. National surveillance will facilitate the collection of uniform clinical, epidemiologic, and laboratory data that can in turn inform prevention messages, ensuring that these high-consequence infections remain rare.

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

1. Utilize standard sources (e.g. reporting*) for case ascertainment for *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM). Standardized surveillance for these infections should use 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 *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM).

Source of data for case ascertainment	Coverage	
	Population-wide	Sentinel sites
Clinician reporting	x	
Laboratory reporting	x	
Reporting by other entities (e.g., hospitals, veterinarians, pharmacies, poison centers)	x	
Death certificates	x	
Hospital discharge or outpatient records		
Extracts from electronic medical records	x	
Telephone survey		
School-based survey		
Other _____Media accounts_____	x	
2016 Template		

2. Utilize standardized criteria for case identification and classification (Sections VI and VII) for *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM) but do not add *Acanthamoeba* Disease (excluding

keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM) 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.

CSTE recommends that all jurisdictions (e.g. States or Territories) with legal authority to conduct public health surveillance follow the recommended methods as outlined above.

Terminology:
* Reporting: process of a healthcare provider or other entity submitting a report (case information) of a condition under public health surveillance TO local or state public health.
**Notification: process of a local or state public health authority submitting a report (case information) of a condition on the Nationally Notifiable Condition List TO CDC.

IV. Goals of Surveillance

The goals of surveillance for *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM) are to monitor the geographic distribution and temporal trends in disease, and to collect standardized epidemiologic and clinical data to better characterize the illnesses and transmission routes to inform control and prevention measures.

V. Methods for Surveillance:

Surveillance for *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM) **should use the recommended sources of data and the extent of coverage listed in Table III.**
Case ascertainment for these infections should use standard sources of data such as those listed in Table III. Additional investigation by state and local health authorities may be required to document possible routes of exposure as this type of information may be lacking in standard data sources. Additionally, media accounts of FLA infections, amebic meningoencephalitis and encephalitis, or “brain-eating ameba” should be considered as sources for case ascertainment and investigated to determine case status.

VI. Criteria for case identification

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

Immediately report all illness to public health authorities that meets any of the following criteria:

1. Any person with clinical signs and/or symptoms consistent with meningoencephalitis or encephalitis, disseminated, or cutaneous disease and who has a positive laboratory test for *N. fowleri*, *B. mandrillaris,* or *Acanthamoeba* spp. These tests may include any of the following:
    a. Detection of *N. fowleri*, *B. mandrillaris,* or *Acanthamoeba* spp. antigen or nucleic acid from a clinical specimen (e.g., immunohistochemical/immunofluorescent staining or PCR)
    b. Visualization of motile amebae in a wet mount of CSF
    c. Isolation of *N. fowleri*, *B. mandrillaris, Acanthamoeba* spp. in culture from a clinical specimen

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

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

Criterion	*Naegleria fowleri* Primary Amebic Meningoencephalitis	*Balamuthia mandrillaris* Disease	*Acanthamoeba* Disease
Clinical Evidence			
Meningoencephalitis or encephalitis	N		

Meningoencephalitis or encephalitis; or disseminated disease; or cutaneous disease; or GAE		N	N
Laboratory Evidence			
Detection of antigen or nucleic acid from a clinical specimen (e.g., immunohistochemical/immunofluorescent staining or PCR)	O	O	O
Visualization of motile amebae in a wet mount of CSF	O	O	O
Isolation of amebae in culture from a clinical specimen	O	O	O
			2016 Template

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" (One or more) 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.
* A requisition or order for any of the "S" laboratory tests is sufficient to meet the reporting criteria.

C. Disease-specific data elements
Below are the disease-specific data elements (n=74) to be collected routinely by all states and territories for each identified case of *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, and *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM).
Clinical information

- Reported symptoms of illness
  - Headache
  - Fever
  - Nausea
  - Vomiting
  - Altered mental status
  - Seizures
  - Other (free text)
- History of non-healing skin lesions or skin disease (Y/N)
- Concurrent or pre-existing conditions patient has currently or in the last 2 years:
  - Immunosuppressant drug or steroid use
  - Alcohol or drug abuse
  - Hematologic malignancy
  - Other cancer
  - HIV/AIDS
  - Autoimmune disease
  - Solid organ transplant
  - Bone marrow transplant
  - Diabetes
  - Renal failure
  - Liver failure
  - Other (free text)

Epidemiologic risk factors

- County/state of suspected exposure
- Number of persons exposed
- Water exposure Y/N

- If Yes, type of water exposure:
  - Canal
  - Lake
  - Pond
  - Ocean
  - River/stream
  - Private club pool
  - Private home pool
  - Fill-and-drain pool
  - Hotel pool
  - Spring (cold or hot)
  - Spa/hot tub/whirlpool
  - Community pool
  - Apartment pool
  - Fountain
  - Water park
  - Drinking water – private source (specify: treated, well, surface, etc.)
  - Drinking water – public source (specify: treated, well, surface, etc.)
- If Yes,
  - Name of water exposure (i.e., name of lake, river, reservoir, beach, etc.)
  - Geospatial coordinates
  - Thermally polluted Y/N
  - Water turbidity: clear, cloudy, murky, unknown
  - Water level: low, normal, high, flood stage, unknown
  - Flow rate: slow, normal, fast, unknown
  - Ambient air temperature at time of exposure (degrees F/C)
  - Water temperature at time of exposure (degrees F/C)
  - Depth of water where exposure occurred

- Water activities Y/N
  - If Yes,
    - Diving into water
    - Inhaled water
    - Jumped into water
    - Swallowed water
    - Splashed water
    - Snorkeling/scuba diving
    - Swimming
    - Water sports (skiing, wakeboarding, etc.)
    - Wore nose clip or plugged nose when jumping/diving
    - Nasal irrigation
      - Neti pot
      - Squeeze bottle
      - Shower nozzle
      - Other device

- Soil exposure Y/N
  - If Yes,
    - Gardening
    - Composting
    - Farm/Ranch
    - Other (specify

- Occupation/Industry/Place of Business exposures, including but not limited to:
  - Farmer/rancher
  - Landscaper
  - Other (specify)
- Travel history in the last 2 years Y/N
  - If yes, specify locations and dates
- Receipt of organs or tissues from persons having confirmed or suspected FLA infection

Laboratory Information

- Method(s) of laboratory testing (culture, PCR, antigen)

- Type of specimen tested (e.g., CSF, brain, skin, other)
- Type of antigen testing (e.g., immunohistochemistry [IHC] or indirect immunofluorescence [IIF])
- Test result
- Molecular characterization of organism (if available)
- Visualization of amebae in CSF

VII. Case Definition for Case Classification

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

1. ***Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM)**

Clinical Criteria
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.

Laboratory Criteria
Confirmatory laboratory evidence:

- Detection of *N. fowleri* antigen or nucleic acid from a clinical specimen (e.g., immunohistochemistry or PCR)

Supportive laboratory evidence:

- Visualization of motile amebae in a wet mount of CSF
- Isolation of *N. fowleri* in culture from a clinical specimen

Epidemiologic Linkage
None specified for case classification

Case Classification
Confirmed case: a case that meets the clinical criteria and confirmatory laboratory criteria for diagnosis
Probable case: a case that meets the clinical criteria and the supportive laboratory criteria for diagnosis

Comment
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. After the onset of symptoms, the disease progresses rapidly and usually results in death within 3 to 7 days.
Patients presenting with the above clinical criteria and found to have a history of recreational freshwater exposure in the two weeks prior to presentation or are known to have performed nasal irrigation (e.g., use of a neti pot for treatment of sinus conditions or practice ritual ablution including nasal rinsing) in the absence of another explanation for their condition, should be investigated further. Urgent confirmatory testing and treatment should be initiated.

2. *Balamuthia mandrillaris* Disease

Clinical Criteria
An infection presenting as meningoencephalitis or encephalitis, disseminated disease (affecting multiple organ systems), or cutaneous disease. 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.

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.

Laboratory Criteria
Confirmatory laboratory evidence:

- Detection of *B. mandrillaris* antigen or nucleic acid or nucleic acid (e.g., immunohistochemistry or PCR) from a clinical specimen (e.g., tissue) or culture.

Epidemiologic Linkage
None specified for case classification

Case Classification
Confirmed case: a case that meets the clinical criteria and confirmatory laboratory criteria for diagnosis

Comment
B. mandrillaris and *Acanthamoeba* spp. can cause clinically similar illnesses and might be difficult to differentiate using commonly available laboratory procedures. Definitive diagnosis by a reference laboratory is required. A negative test on CSF does not rule out *B. mandrillaris* infection because the organism is not commonly present in the CSF. Once the disease progresses to neurologic infection, it is generally fatal within weeks or months; however, a few patients have survived this infection.
Patients presenting with the above clinical criteria who have received a solid organ transplant should be further investigated to determine if the infection was transmitted through the transplanted organ. An investigation of the donor should be initiated through notification of the organ procurement organization (OPO) and transplant center.

3. *Acanthamoeba* Disease (excluding keratitis)

Clinical Criteria
An infection presenting as meningoencephalitis or encephalitis, disseminated disease (affecting multiple organ systems), or cutaneous disease. *Acanthamoeba* spp. GAE presents similarly to *B. mandrillaris* GAE with early personality and behavioral changes, depressed mental status, fever, photophobia, seizures, nonspecific cranial nerve dysfunction, and visual loss. Skin lesions and sinus disease may also be seen.

Laboratory Criteria
Confirmatory laboratory evidence:

- Detection of *Acanthamoeba* spp. antigen or nucleic acid (e.g., immunohistochemistry or PCR) from a clinical specimen (e.g., tissue) or culture.

Epidemiologic Linkage
None specified for case classification

Case Classification
Confirmed case: a case that meets the clinical criteria and confirmatory laboratory criteria for diagnosis

Comment
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. 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*). A negative test on CSF does not rule out *Acanthamoeba* spp. infection because the organism is not commonly present in the CSF.

Although it is unknown if *Acanthamoeba* spp. can be transmitted via organ transplantation, patients presenting with the above clinical criteria who have received a solid organ transplant should be further investigated to determine if the infection was transmitted through the transplanted organ. An investigation of the donor should be initiated through notification of the organ procurement organization (OPO) and transplant center.

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
None specified.

B. Classification Tables
Confirmed Case: a case that meets the confirmed laboratory criteria for diagnosis
Probable Case: a case that meets the supportive laboratory criteria for diagnosis

Table VII-B. Criteria for defining cases of *Acanthamoeba* Disease (excluding keratitis), *Balamuthia mandrillaris* Disease, or *Naegleria fowleri* causing Primary Amebic Meningoencephalitis (PAM).

Criterion	*Naegleria fowleri* causing PAM, Probable	*Naegeleria fowleri* causing PAM, Confirmed	*Balamuthia mandrillaris* disease, Confirmed	*Acanthamoeba, spp*, Confirmed
Clinical Evidence				
Meningoencephalitis or encephalitis	N	N		
Meningoencephalitis or encephalitis; or disseminated disease; or cutaneous disease; or GAE			N	N
Laboratory evidence				
Detection of antigen or nucleic acid from a clinical specimen (e.g., immunohistochemistry or PCR)		N	N	N
Visualization of motile amebae in a wet mount of CSF	O			
Isolation of amebae in culture from a clinical specimen	O			

Notes:
S = This criterion alone is Sufficient to classify a case.
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). If the absence of a criterion (i.e., criterion NOT present) is required for the case to meet the classification criteria, list the Absence of criterion as a Necessary component.
O = At least one of these “O” (One or more) 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 classify a case. (These “O” 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.) A number following an “O” indicates that this criterion is only required for a specific disease/condition subtype.

VIII. Period of Surveillance
Surveillance should be ongoing.

IX. Data sharing/release and print criteria

- Data will be used to determine the burden of illness due to these infections, monitor trends in illness over time, identify novel transmission routes, assess the effectiveness of control measures, and monitor progress in prevention.
- Information may be distributed among states and territories or to CDC according to jurisdiction specific protocols. Unusual situations may increase the need for communication. For example, multi-state investigation of transplant-related infections might require sharing of data among health departments and/or state and federal agencies in several jurisdictions involved in investigations.
- State-specific data on cases, if shared with CDC, will be verified prior to publication.
- Only de-identified case data will be released by CDC to the general public

X. Revision History

Position Statement ID	Section of Document	Revision Description
16-ID-12	Statement of the Problem; Background and Justification	Language recommending these conditions be added to be NNC list has been removed to reflect the decision and vote of the Council at the 2016 CSTE Business Meeting to NOT add the conditions to the NNC list.
11-ID-15	VII. Case Definition for Case Classification	Isolation in culture will no longer be used to define a confirmed case, for each condition. Detection of antigen or nucleic acid in a clinical specimen is required to classify a case as confirmed, for each condition.

XI. References

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