

Epidemiology and Clinical Characteristics of Primary Amebic Meningoencephalitis Caused by *Naegleria fowleri*: A Global Review

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Background. Primary amebic meningoencephalitis (PAM) is a rapidly progressive and often fatal condition caused by the free-living ameba *Naegleria fowleri*. To estimate the global occurrence, characterize the epidemiology, and describe the clinical features of PAM, we report a series of PAM cases published in the international literature and reported to the Centers for Disease Control and Prevention (CDC).

Methods. We performed a literature search of PAM case reports published through 2018. Additionally, we included cases reported through the CDC's Free-Living Ameba surveillance or diagnosed via CDC's Free-Living and Intestinal Amebas Laboratory. Cases were classified as confirmed, probable, or suspect on the basis of confirmatory testing, presentation, exposure, and disease course.

Results. A total of 381 PAM cases were identified. Seven reported survivors were classified as confirmed. The most commonly reported exposure associated with PAM was swimming/diving, and the most common class of water source was lakes/ponds/reservoirs. Patients were predominantly male (75%), with a median age of 14 years. Confirmed and probable cases were similar in their survival, course of illness, and cerebrospinal fluid (CSF) findings.

Conclusions. PAM is a rare but deadly disease with worldwide occurrence. Improved clinician awareness, resulting in earlier diagnosis and treatment, may contribute to increased survival among PAM patients. The case definition of probable used in this study appears to capture cases of PAM, as evidenced by similarities in outcomes, clinical course, and CSF profile to confirmed cases. In the absence of confirmatory testing, clinicians could use this case definition to identify cases of PAM.

Keywords. *Naegleria fowleri*; free-living ameba; primary amebic meningoencephalitis.

Primary amebic meningoencephalitis (PAM) is a rapidly progressive and often fatal condition caused by the free-living ameba *Naegleria fowleri*. Thermophilic in nature, *N. fowleri* is commonly found in warm freshwater environments [1]. PAM occurs upon accidental introduction of *N. fowleri* into the nose, after which the ameba invades the central nervous system (CNS) through the cribriform plate and olfactory nerves [2]. Invasion of the CNS results in cerebral edema, necrosis, herniation, and, in most cases, death [3]. A presumptive diagnosis of *N. fowleri* infection can be made by microscopic examination of the cerebrospinal fluid (CSF) or brain tissue [4], and a definitive diagnosis can be made by immunohistochemistry (IHC), indirect immunofluorescence (IIF) [5], polymerase chain reaction (PCR) [6], or next-generation sequencing (NGS) [7].

The Centers for Disease Control and Prevention (CDC) conducts passive surveillance for PAM in the United States. Since establishment of the surveillance system in 1962, 145 cases of PAM have been reported in the United States, largely from southern states [8]. Cases occur primarily in summer months and among young males, with the majority of exposures associated with recreational water use in freshwater bodies such as lakes and rivers [9]. Additionally, 3 US cases have been associated with nasal irrigation or ritual nasal ablution using tap water: 2 cases were reported from Louisiana [10] and 1 was reported from the US Virgin Islands [11].

Naegleria fowleri has been detected on every continent except Antarctica [12]. Cases are rare; recent estimates of the total worldwide number of reported PAM cases have been 235 [12] and 260 cases [13]. To provide an updated estimate of the global occurrence, characterize the epidemiology, and describe the clinical features of PAM, we present a series of PAM cases published in the international literature and those reported to CDC.

METHODS

Literature Search

We searched Medline, EMBASE, and Ovid Global Health for reports published as of 31 December 2018 with the search terms

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“*Naegleria fowleri*,” “amebic meningoencephalitis,” and related terms. Two independent reviewers screened titles and abstracts for relevance. Additional reports were identified by reviewing the references listed in each publication. To be included, publications were required to have at least an abstract available in English. We added data for US cases captured through the CDC’s Free-Living Ameba Surveillance System as described in Capewell [14], as well as 2 cases outside the United States confirmed through CDC’s Free-Living and Intestinal Amebas Laboratory. The following information was extracted for each case when provided: demographic characteristics, clinical signs on presentation, exposure source, exposure date and location, illness duration and timeline, CSF profile, diagnosis timing and method, treatment, and outcome.

Case Classification

Cases were classified as confirmed if *N. fowleri* was identified in CSF or brain tissue using IHC, IIF, PCR, or NGS. Cases were classified as probable or suspect if there was identification of *N. fowleri* in CSF or brain tissue by direct visualization (eg, wet mount or hematoxylin and eosin stain) or ameba culture but no confirmatory molecular diagnosis was available. Of these cases, those that had an acute-onset, rapidly progressive meningoencephalitis characterized by fever, headache, vomiting, and/or meningismus within 14 days of water exposure were classified as probable. All other cases with *N. fowleri* identification by direct visualization or ameba culture were classified as suspect.

Additionally, cases were categorized into 2 groups on the basis of their signs and symptoms on initial presentation to a healthcare facility, as described in Capewell [14]. Cases were categorized in the early group if presenting with vague symptoms resembling a flu-like prodrome and in the late group if presenting with signs of CNS involvement.

Finally, cases were categorized as receiving either antemortem or postmortem diagnoses. Diagnoses were classified as antemortem if *N. fowleri* was the suspected cause of meningoencephalitis based on microscopic visualization or confirmatory testing prior to the patient’s death or discharge. Cases were classified as postmortem if *N. fowleri* was not suspected or tested for as the cause of meningoencephalitis prior to death.

Statistical Analyses

Cases were mapped by country of exposure using ArcMap version 10.5 GIS software. Negative binomial regression analysis was conducted to assess for trends in annual case counts and was restricted to 1965 (the year of the first published case report [15]) through 2016 (accounting for a 2-year delay to publication). Comparisons among classification groups (confirmed vs probable and confirmed vs suspect) were conducting using Wilcoxon-Mann-Whitney tests (continuous variables) or Pearson χ^2 tests (categorical variables). Data were analyzed using SAS 9.4 (SAS Inc., Cary, NC).

RESULTS

A total of 381 cases of PAM caused by *N. fowleri* were identified. The literature search identified 223 non-US cases (Supplementary Table 1). Additionally, 145 US cases were identified through CDC’s Free-Living Ameba Surveillance System (1962–2018) and 11 US cases were identified through case reports before 1962. Two cases, from Bangladesh [16] and Australia (unpublished data), were identified through diagnostic testing at CDC’s Free-Living and Intestinal Amebas Laboratory. Of the 381 cases, 182 were classified as confirmed, 89 were probable, and 110 were suspect. Case exposures occurred in 33 countries (Figure 1). The greatest number of case exposures were reported in the United States (41%), Pakistan (11%), and Mexico (9%).

Reported cases occurred from 1937 through 2018. The median time from case occurrence to report publication was 2 years. Thus, negative binomial regression was restricted to 1965 (the year of the first published case report [15]) through 2016 (accounting for the 2-year delay to publication). From 1965 to 2016, the total number of reported PAM cases increased an average of 1.6% per year (95% confidence interval [CI], .6%–2.6%; $P = .002$). During this period, the number of confirmed PAM cases increased an average of 4.5% per year (95% CI, 2.9%–6.1%; $P < .0001$), but there was no trend detected in the number of probable or suspect cases (Figure 2).

The timing of diagnosis (antemortem vs postmortem) was reported for 283 cases. From 1965 to 2016, the number of cases with antemortem diagnoses increased an average of 3.6% per year (95% CI, 2.0%–5.2%; $P < .0001$); however, there was no trend detected in the number of cases with postmortem diagnoses (Figure 3). Of 181 cases with antemortem diagnoses, 88 (49%) were diagnosed by direct visualization alone, 25 (14%) were confirmed by IHC or IIF, and 61 (34%) were confirmed by PCR or NGS. Of 102 cases with postmortem diagnoses, 59 (58%) were diagnosed by direct visualization alone, 17 (17%) were confirmed by IHC or IIF, and 21 (21%) were confirmed by PCR or NGS. Of 85 cases diagnosed by PCR (61 antemortem diagnosis, 21 postmortem diagnosis, and 3 with unknown diagnostic timing), 72 (85%) used the CDC multiplex real-time PCR assay for simultaneous detection of *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri* [6].

Of the 247 cases with reported water activities thought to result in *N. fowleri* exposure, the most common activities were swimming/diving (58%), bathing (16%), water sports (eg, waterskiing, wakeboarding, jet skiing; 10%), and nasal irrigation (9%; Table 1). Of the 265 cases with reported water sources that were thought to result in *N. fowleri* exposure, the most common sources were lakes/ponds/reservoirs (45%), swimming pools (13%), tap water (12%), and canals/ditches/puddles (12%; Table 1). The percentage of exposures attributed to various water activities and water sources differed between US and non-US cases (Supplementary Table 2); however, swimming/



Figure 1. Reported cases of primary amebic meningoencephalitis (n = 381) by country of exposure. No cases were reported from the US states of Alaska and Hawaii nor from countries not pictured in the Western Pacific Region.

diving remained the most common exposure activity. Of 34 cases associated with swimming pools, 33 (97%) occurred in 1987 or earlier. Of the 315 cases reporting the season of exposure, 85% described the season as warm, hot, or summer.

Patients were predominantly male (75%), with a median age of 14 years (range, 1 month–85 years; [Table 2](#)). The median age among cases in the United States (12 years) was slightly lower than that of non-US cases (15 years; [Supplementary Table 3](#)). The overall case-fatality rate was 92% with 32 reported survivors; however, only 7 survivors met laboratory criteria for confirmed classification. The case-fatality rate differed between confirmed and suspect cases (96% vs 77%; $P < .001$; [Table 2](#)) and between US cases and non-US cases (98% vs 87%; $P < .001$; [Supplementary Table 3](#)).

The median incubation period for cases was 6 days (range, 1–30; [Table 2](#)). The incubation period was shorter for confirmed cases (median, 5 days; range, 1–12) compared with suspect cases (median, 7 days; range, 1–30; $P < .001$). The overall median time from onset of symptoms to initiation of PAM-specific

treatment was 3.5 days (range, 0–49); this median was shorter for confirmed cases (3 days) compared with probable cases (5 days; $P < .001$) and suspect cases (17 days; $P = .007$). Similarly, the overall median time from hospitalization to initiation of PAM-specific treatment was 1 day (range, 0–43); this median was shorter for confirmed cases (0 days) compared with probable cases (2 days; $P = .017$) and suspect cases (5.5 days; $P < .001$). The overall median duration of hospital stay was 3 days for decedents (range, 0–53) and 30 days for survivors (range, 7–150). Last, the overall median time from onset of symptoms to death was 5 days (range, 1–65).

In total, 256 cases were reported with sufficient details to determine the patient's clinical status on initial presentation to a healthcare facility. Of these patients, 41 (16%) presented with early, flu-like prodromal symptoms only, and 215 (84%) presented with late symptoms indicating CNS involvement ([Table 3](#)). There was no difference in symptom group on presentation (early vs late) by class ($P = .1194$). Overall, the most common symptoms on presentation were fever (88%), headache

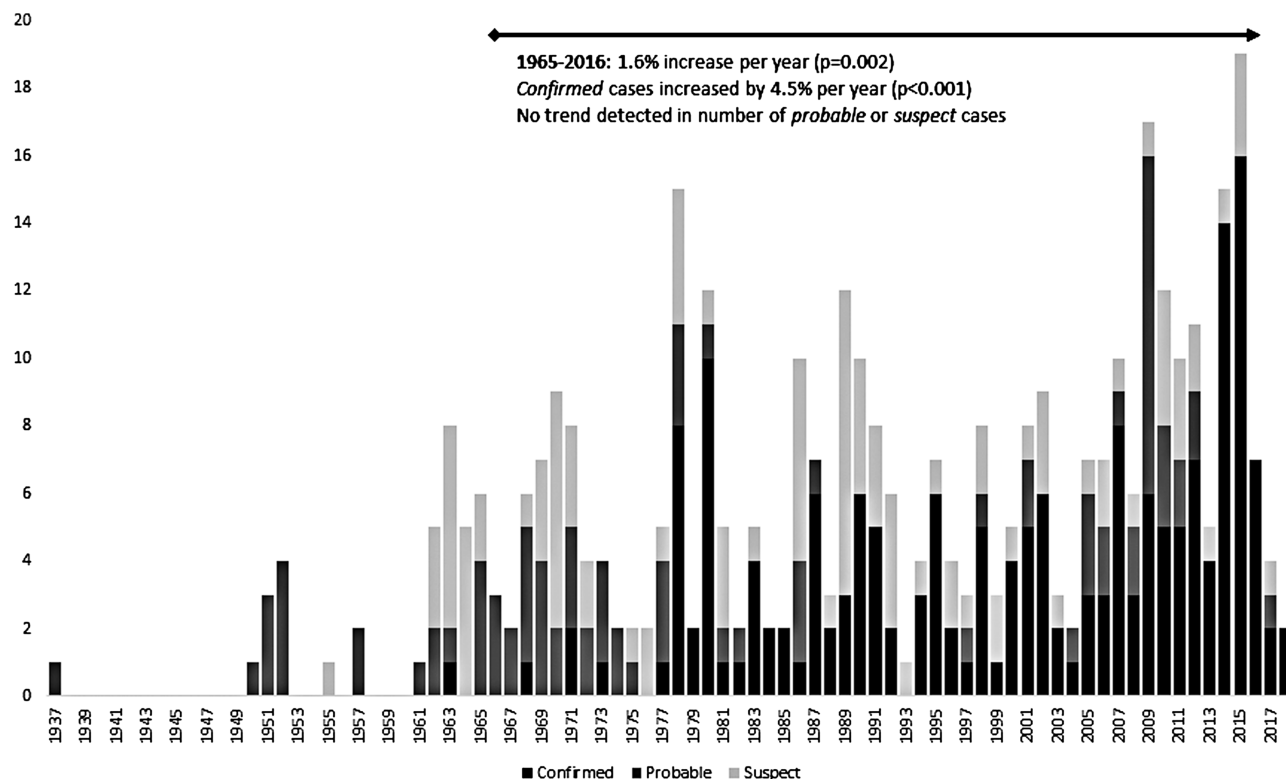


Figure 2. Reported cases of primary amebic meningoencephalitis ($n = 381$) by case year and classification. Negative binomial regression was restricted to 1965 (the year of the first published case report [12]) through 2016 (accounting for the median 2-year delay to publication). Cases that occurred in 2017 and 2018 were likely underreported due to this delay in publication.

(82%), nausea/vomiting (57%), altered mental status (50%), and nuchal rigidity (35%). Thirty-four patients (13%) presented in an advanced state with coma.

CSF findings were reported for 237 patients (Table 4). Overall, opening pressures were elevated (median, 290 mm H₂O; range, 36–570) and red blood cell counts were elevated (median, 212 cells/ μ L; range, 0–30 750). White blood cell counts were also elevated (median, 1238 cells/ μ L; range 0–30 000); these were predominantly neutrophils (median, 82%; range, 0%–100%). The CSF of most patients was characterized by elevated protein (median, 326 mg/dL; range, 20–1374) and low glucose (median, 29 mg/dL; range, 0–223). Compared with confirmed cases, suspect cases had fewer white blood cells ($P < .001$), a greater percentage of lymphocytes ($P < .001$), lower protein ($P < .001$), and higher glucose ($P = .035$). The CSF profile of probable cases was similar to that of confirmed cases but had a greater percentage of neutrophils ($P = .002$).

Among 254 PAM cases with treatment histories provided, the most common medications administered were amphotericin B (71%); azoles including miconazole, ketoconazole, itraconazole, voriconazole, and fluconazole (40%); rifampin (28%); injectable corticosteroids (20%); azithromycin (14%); and miltefosine (9%). The majority of patients (75%) were empirically treated

with antibiotics on presentation due to suspicion of bacterial meningitis.

Among the 7 PAM survivors with a confirmed diagnosis [19–24], the following medications were used for treatment: intravenous amphotericin B (7/7), intrathecal amphotericin B (5/7), azoles (6/7), rifampin (6/7), azithromycin (4/7), miltefosine (4/7), and dexamethasone (5/7). The median time from symptom onset to treatment was 2.5 days (range, 0–5; Table 5). The 4 US survivors received deoxycholate (conventional, nonliposomal) formulations of amphotericin B; formulations for the 3 international survivors were unknown.

DISCUSSION

In this review, we identified 381 global PAM cases; however, this is likely an underestimate of the true worldwide occurrence of PAM. A prior study estimated approximately 16 PAM cases in the United States per year [25], though only 0–8 are reported annually [9]. It is difficult to extrapolate this underestimate to other countries. The number of undiagnosed cases may be even higher in countries that do not have a surveillance system for PAM or available diagnostic testing. Of the 381 reported cases, 156 (41%) were reported from the United States, likely due to

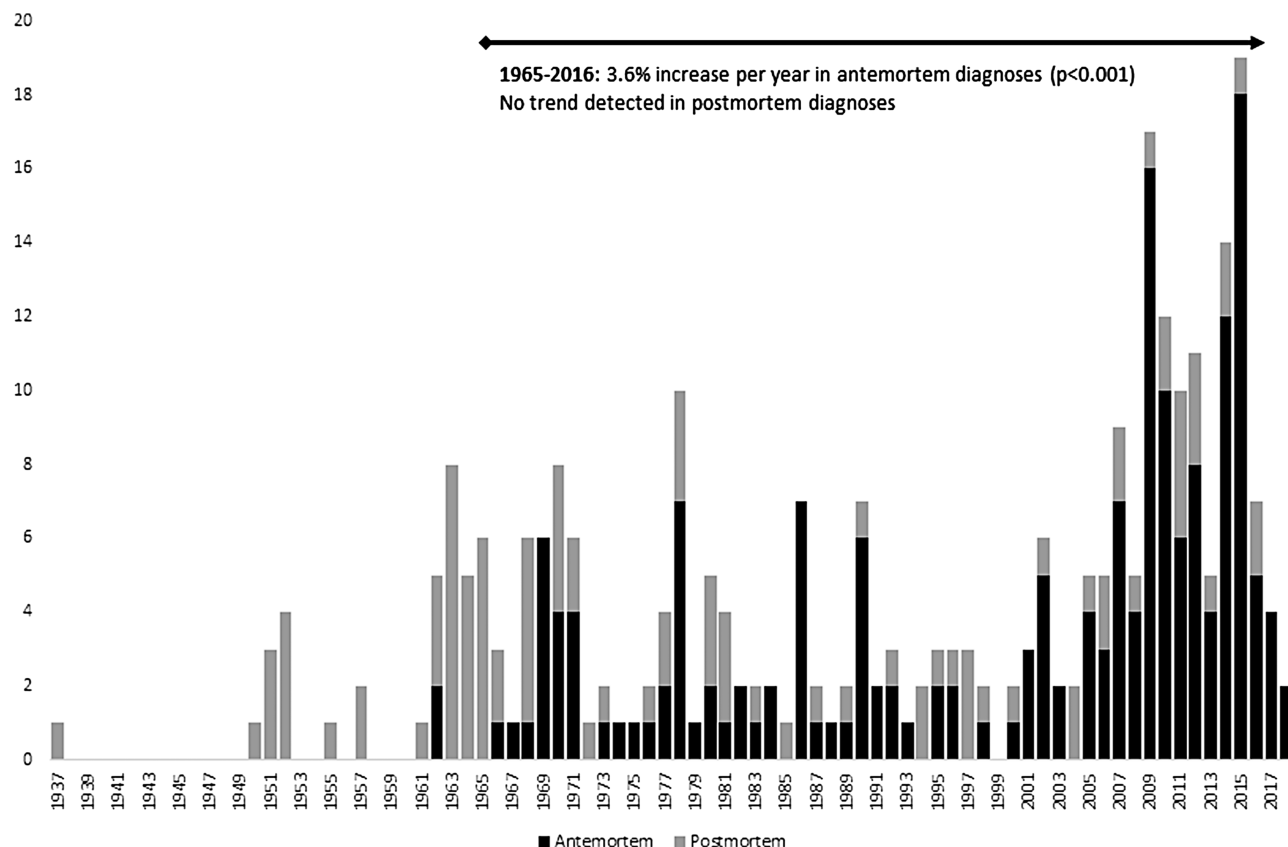


Figure 3. Reported cases of primary amebic meningoencephalitis (n = 283) by case year and timing of diagnosis (antemortem vs postmortem). Negative binomial regression was restricted to 1965 (the year of the first published case report [12]) through 2016 (accounting for the median 2-year delay to publication). Cases that occurred in 2017 and 2018 were likely underreported due to this delay in publication.

Table 1. Probable Water Exposures—Activity and Water Source—for Reported Cases of Primary Amebic Meningoencephalitis

Exposure and Category	n (%)
Water activity (N = 247)	
Swimming/diving	143 (58)
Bathing ^a	40 (16)
Water sports (eg, waterskiing, wakeboarding, jet skiing)	24 (10)
Nasal irrigation	22 (9)
Splashing	12 (5)
Water festival	2 (1)
Other	4 (2)
Water source (N = 265)	
Lake/pond/reservoir	119 (45)
Swimming pool ^b	34 (13)
Tap water ^c	32 (12)
Canal/ditch/puddle	32 (12)
River/stream	21 (8)
Geothermal water	20 (8)
Water tank/cistern	5 (2)
Aquatic sports venue	2 (1)

^aDepending on the setting, the term “bathing” may be used to refer to cleaning oneself or swimming. It was not possible to distinguish these definitions from case reports.

^bDetailed information regarding the operation, management, and condition of the pool at the time of the case-patient exposure was not reported for most cases. Where information was provided, pools did not meet recommended chlorine levels (<https://www.cdc.gov/healthywater/swimming/residential/disinfection-testing.html>) [17] or structural issues were identified [18].

^cTap water includes water obtained through public water systems (n = 24), wells (n = 6), or boreholes (n = 2).

surveillance bias. Although PAM is not a nationally notifiable disease in the United States, CDC maintains a registry of US PAM cases, supplemented with laboratory diagnostic capacity through CDC’s Free-Living and Intestinal Amebas Laboratory.

The observed increase in global PAM cases over time is likely due to improvements in awareness and diagnostic capacity. Confirmed cases increased from 1975 to 2016, suggesting that confirmatory diagnosis, such as the multiplex PCR assay for *N. fowleri* and other free-living amebas, may have become more readily available in recent years and may be increasingly used for patients for whom PAM is suspected as a cause of meningoencephalitis. Additionally, antemortem diagnoses increased over time; this suggests improvements in clinician awareness and early recognition of PAM.

Some have proposed that global changes in temperature and climate may further drive an increase in PAM incidence [26–28]. The majority of case exposures (85%) were specifically reported during warm, hot, or summer seasons, consistent with the thermophilic nature of *N. fowleri* [1]. The true proportion of cases exposed in a warm climate likely exceeds 85%, as the level of detail included in reports was variable and many cases were reported in tropical regions of the world where the climate may be warm year-round. Analysis of the specific geographic

Table 2. Demographics and Clinical Course for Reported Cases of Primary Amebic Meningoencephalitis (N = 381), by Classification

Characteristic	Total (N = 381)	Confirmed (n = 182)		Probable (n = 89)		Suspect (n = 110)	
	Value	Value	PValue	Value	PValue ^a	Value	PValue ^b
Median age (range)	(n = 372) 14 y (1 mo–85 y)	(n = 180) 12 y (4 mo–75 y)	Ref	(n = 88) 16 y (5 mo–64 y)	.209	(n = 104) 13 y (1 mo–85 y)	.986
Sex, n (%)	(n = 371)	(n = 181)		(n = 86)		(n = 04)	
Male	278 (75)	141 (78)		66 (77)		71 (68)	
Female	93 (25)	40 (22)	Ref	20 (23)	.876	33 (32)	.091
Outcome, n (%)	(n = 380)	(n = 182)		(n = 89)		(n = 109)	
Died	348 (92)	175 (96)		89 (100)		84 (77)	
Survived	32 (8)	7 (4)	Ref	0 (0)	.100	25 (23)	<.001
Median (range) incubation period, days	(n = 113) 6 (1–30)	(n = 62) 5 (1–12)	Ref	(n = 24) 6 (1–21)	.111	(n = 27) 7 (1–30)	<.001
Median (range) time from onset of symptoms to initiation of PAM-specific treatment, days	(n = 73) 3.5 (0–49)	(n = 44) 3 (0–11)	Ref	(n = 14) 5 (2–10)	.007	(n = 15) 17 (0–49)	<.001
Median (range) time from hospitalization to initiation of PAM-specific treatment, days	(n = 84) 1 (0–43)	(n = 45) 0 (0–12)	Ref	(n = 19) 2 (0–8)	.017	(n = 20) 5.5 (0–43)	<.001
Median (range) duration of hospital stay, days	(n = 256)	(n = 138)		(n = 77)		(n = 41)	
Decedents	3 (0–53)	3 (0–25)	Ref	2 (0–18)	.005	3 (0–53)	.149
Survivors	30 (7–150)	29 (19–76)	Ref	N/A	N/A	30 (7–150)	.978
Median (range) time from onset of symptoms to death, days	(n = 253) 5 (1–65)	(n = 122) 5 (1–18)	Ref	(n = 74) 5 (1–23)	.884	(n = 57) 6 (1–65)	.237

P values <.05 are represented in bold text.

Abbreviations: N/A, not applicable; PAM, primary amebic meningoencephalitis.

^aProbable vs confirmed cases by Wilcoxon-Mann-Whitney test (continuous variables) or Pearson χ^2 (categorical variables) test.

^bSuspect vs confirmed cases by Wilcoxon-Mann-Whitney test (continuous variables) or Pearson χ^2 (categorical variables) test.

distributions of cases within countries, such as the predominance of cases in southern states in the United States, could aid in understanding climate-related variability in risk.

The age and sex of patients were generally consistent with those previously described in the United States [9]. Overall, cases predominantly occurred in young males. This demographic group may be more likely to engage in activities that may result in high-risk *N. fowleri* exposure [9] or may be predisposed due to sex-linked hormones as has been hypothesized for other infections such as *Entamoeba histolytica* liver abscesses [29]. Additionally, suspicion and consequent diagnosis of PAM in young male patients may also be high due to clinician awareness of these demographic trends or potential sex-related disparities in access to healthcare. Non-US cases were slightly older than US cases; this may be due to greater prevalence of behaviors such as nasal irrigation among adults in non-US settings.

The routes of exposure commonly identified among PAM cases suggest several practices that may be targeted for prevention. Reported PAM cases were most commonly associated with recreational water use, consistent with common exposures previously reported among US cases [9]. As *N. fowleri* naturally lives in freshwater environments, prevention messages should emphasize avoidance of getting water up the nose while engaging in recreational water activities in untreated freshwater.

Though *N. fowleri* should not survive in a properly cleaned, maintained, and disinfected swimming pool [9], swimming pools represented the second most common water source

among reported PAM cases. Detailed information regarding the operation, management, and condition of pools at the time of the patient exposure was not reported for most cases. Where information was provided, pools did not meet standards for maintenance and disinfection. Several of these pools were thought to be inadequately chlorinated [17], and a later investigation of one particular pool associated with 16 cases in the Czech Republic revealed cracks in the pool wall from which *Naegleria* were cultured [18]. Of 34 cases associated with swimming pools, only 1 occurred after 1987; this case occurred in the United States in 2015 and was associated with an untreated pool. Though *N. fowleri* exposure from swimming pools may be less common in recent decades, prevention messages regarding chlorination and management of swimming pools may further decrease the burden of PAM.

Additionally, 9% of cases were associated with nasal irrigation, presenting an opportunity for prevention messages about boiling and/or treating water used for religious or therapeutic nasal irrigation [10, 30]. Similarly, additional targeted messages may be developed to focus on other high-risk exposures unique to different cultural settings, such as water splashing festivals, where 2 reported cases were thought to have been exposed [7, 31].

Among the 381 PAM cases identified in this review, 32 survivors were reported; however, only 7 met laboratory criteria for confirmed classification. The remainder of survivors were classified as suspect, meaning that their presentation, exposure,

Table 3. Clinical Signs on Initial Presentation to a Healthcare Facility for Reported Cases of Primary Amebic Meningoencephalitis (N = 256) by Classification

Group and Symptoms	Total (N = 256) n (%)	Confirmed (n = 131) n (%)	Probable (n = 75) n (%)	Suspect (n = 50) n (%)
Early (flu-like prodrome only)	41 (16)	27 (21)	8 (11)	6 (12)
Fever	226 (88)	113 (86)	68 (91)	45 (90)
Headache	209 (82)	111 (85)	64 (85)	34 (68)
Nausea/vomiting	147 (57)	80 (61)	41 (55)	26 (52)
Fatigue/lethargy	65 (25)	44 (34)	17 (23)	4 (8)
Respiratory	19 (7)	7 (5)	7 (9)	5 (10)
Late (central nervous system involvement)	215 (84)	104 (79)	67 (89)	44 (88)
Altered mental status	128 (50)	70 (53)	34 (45)	24 (48)
Nuchal rigidity	90 (35)	38 (29)	34 (45)	18 (36)
Seizures	55 (21)	25 (19)	23 (31)	7 (14)
Coma	34 (13)	10 (8)	14 (19)	10 (20)
Photophobia	29 (11)	20 (15)	4 (5)	5 (10)
Drowsiness	22 (9)	12 (9)	8 (11)	2 (4)
Kernig's/Brudzinski's sign	22 (9)	3 (2)	6 (8)	13 (26)
Extremity weakness	11 (4)	5 (4)	3 (4)	3 (6)
Blurred vision	10 (4)	3 (2)	6 (8)	1 (2)
Abnormal gait	8 (3)	4 (3)	0 (0)	4 (8)
Cranial nerve abnormalities	8 (3)	2 (2)	4 (5)	2 (4)
Sensory abnormalities	7 (3)	1 (1)	2 (3)	4 (8)

or disease course was not consistent with the expected clinical picture and epidemiology for PAM as described above. It is possible that other amebae such *Acanthamoeba* spp. or other etiologies could have caused some of these surviving cases. Without access to confirmatory testing in many settings, diagnosis can be difficult.

All 7 confirmed survivors received amphotericin B, and the majority received azoles, rifampin, azithromycin, miltefosine, and/or dexamethasone. Factors that contributed to patient survival likely include use of this recommended combination of antimicrobials, early identification and treatment, and application of traumatic brain injury principles for management of elevated intracranial pressure. Unfortunately, amphotericin B alone is not universally effective, as it was administered to nearly three-quarters (71%) of PAM patients. The formulation

of amphotericin B (eg, deoxycholate vs lipid or liposomal) may play a role in treatment effectiveness, as conventional deoxycholate formulations have shown greater efficacy in vitro and in mouse models, despite greater adverse effects [14]. Additionally, amphotericin B and the other drugs included in survivors' regimens may not be available in all settings; multiple case reports specifically mentioned unavailability of amphotericin B at the time of patient presentation and diagnosis [32, 33]. Global efforts to control PAM mortality should focus on improving access to treatment, as well as promoting early recognition and treatment by clinicians. The majority of patients presented with late signs indicating CNS involvement, rather than with early signs. This is not surprising as PAM may not often be considered as a differential diagnosis for vague, flu-like symptoms and patients may not choose to seek care

Table 4. Initial Cerebrospinal Fluid Laboratory Findings on Admission for Reported Cases of Primary Amebic Meningoencephalitis (N = 237) by Classification

Test (Reference Value)	Total (N = 237)		Confirmed (n = 118)			Probable (n = 80)			Suspect (n = 39)		
	n	Median (Range)	n	Median (Range)	P Value	n	Median (Range)	P Value ^a	n	Median (Range)	P Value ^b
Opening pressure (100–200 mm H ₂ O)	31	290 (36–570)	11	380 (36–530)	Ref	14	255 (138–570)	.261	6	215 (55–500)	.312
Red blood cell count (0 cells/μL, CSF)	124	212 (0–30 750)	87	212 (0–30 750)	Ref	29	350 (0–24 600)	.392	8	756 (0–2600)	.545
White blood cell count (0–5 cells/μL)	232	1238 (0–30 000)	117	1830 (10–29 000)	Ref	78	1510 (7–30 000)	.296	37	415 (0–22 000)	< .001
% Neutrophils (2% ± 5%)	181	82 (0–100)	97	80 (12–100)	Ref	64	90 (15–100)	.002	20	73 (0–100)	.104
% lymphocytes (62% ± 34%)	128	20 (2–100)	72	20 (2–90)	Ref	38	15 (2–85)	.691	18	65 (5–100)	< .001
Protein (15–60 mg/dL)	215	326 (20–1374)	109	326 (24–1342)	Ref	70	361 (20–1374)	.978	36	115 (20–731)	< .001
Glucose (40–80 mg/dL)	208	29 (0–223)	106	29 (0–180)	Ref	69	22 (0–223)	.401	33	42 (0–185)	.035

P values < .05 are represented in bold text.

^aProbable vs confirmed cases by Wilcoxon-Mann-Whitney test.

^bSuspect vs confirmed cases by Wilcoxon-Mann-Whitney test.

Table 5. Treatment of Confirmed Survivors of Primary Amebic Meningoencephalitis (n = 7)

Ref.	Country of Exposure	Year	Age (y)	Sex	Amphotericin B Route, Duration, days	Azole Route, Duration, days ^a	Azithromycin Route, Duration, days	Miltefosine Route, Duration, days	Rifampin Route, Duration, days	Dexamethasone Route, Duration, days	Symptom Onset to Start of Treatment, days
[19]	Australia	1971	14	M	IV (Unk.) ^b IT (Unk.) ^b	...	...	...	...	...	Unk.
[20]	United States	1978	9	F	IV (9) IT (10)	IV (9) IT (9)	...	...	PO (9)	IV (Unk.) ^b	3
[21]	Mexico	2003	10	M	IV (14)	IV/PO (30) ^c	...	...	PO (30)	IV (Unk.) ^b	0
[22]	United States	2013	12	F	IV (26) IT (10)	IV (26)	IV (26)	PO (26)	IV (26)	IV (4)	2
[23]	United States	2013	8	M	IV (19) IT (5)	IV (19)	PO (19)	PO (19)	PO (19)	IV (29)	5
[24]	Pakistan	2015	25	M	IV (Unk.) ^b IT (Unk.) ^b	Unk. ^d (Unk.) ^b	Unk. ^d (Unk.) ^b	PO (Unk.) ^b	IV (Unk.) ^b	...	3
N/A ^e	United States	2016	16	M	IV (14) IT (10)	IV (28)	IV (28)	PO (28)	IV/PO (28) ^c	IV (4)	2

Abbreviations: IT, intrathecal; IV, intravenous; N/A, not applicable; PO, oral; Unk., unknown.

^aThis included miconazole (n = 1 patient) and fluconazole (n = 5 patients).

^bDuration of treatment unknown.

^cCombination of intravenous and oral administration; specific duration of each route unknown.

^dRoute of administration unknown.

^eNot applicable; manuscript in preparation.

for mild symptoms. Improved clinician awareness is critical for early diagnosis and treatment, in light of this rapid progression and often advanced presentation.

Confirmed cases were generally characterized by a more rapid clinical course compared with suspect cases. Consequently, rapid progression of meningoencephalitis in a patient should raise a clinician index of suspicion for PAM. CSF findings for confirmed and probable cases were consistent with those previously reported in the United States [14]. Though these CSF findings alone may not be sufficient to allow clinicians to distinguish PAM from other infectious causes of meningitis, the presence of predominantly neutrophilic elevated white blood cell count, increased protein, and low glucose should trigger suspicion for PAM in addition to bacterial meningitis. The majority of cases were empirically treated with antibiotics, which is logical as bacterial meningitis is a more common etiology for meningoencephalitis than PAM. Many unreported cases of PAM were also likely treated with antibiotics and were misdiagnosed as bacterial meningitis.

This study is subject to several limitations. First and most importantly, not all PAM cases are recognized and reported, and thus these reports likely represent a small fraction of the total number of PAM cases. Second, the quality of the reports was inconsistent, as they spanned several decades and numerous journals. Only English-language texts were included, and not all full texts could be acquired; some case data were abstracted from abstracts only. Finally, access to confirmatory diagnostic testing for PAM is/was not feasible in many settings. Thus, the classification technique used to

designate confirmed cases may be biased in favor of higher-resource settings.

Ultimately, PAM is a disease with worldwide occurrence, though rare. We hope that summarizing the epidemiology and clinical features of global PAM cases will assist clinicians in developing greater awareness of PAM. The probable case definition used in this study (acute-onset, rapidly progressive meningoencephalitis characterized by fever, headache, vomiting, and/or meningismus within 14 days of water exposure) appears to capture cases of PAM, as evidenced by similarities in outcome, clinical course, clinical presentation, and CSF profile to laboratory-confirmed cases. In the absence of confirmatory testing, clinicians could use these criteria to identify cases of PAM.

Experts at the CDC are available 24/7 to provide diagnostic and clinical assistance to clinicians who suspect PAM in a patient. The CDC Emergency Operations Center can be contacted at 770-488-7100. For cases outside the United States, consultations can be coordinated through the clinician's Ministry of Health. Confirmatory testing of international clinical samples may be available through the CDC Free-Living and Intestinal Amebas Laboratory. By engaging institutions and clinicians internationally, we hope to increase awareness and capacity to recognize, diagnose, and treat PAM.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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