

Review Article

Primary Amoebic Meningoencephalitis: A Global Health Threat or Localized Problem

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A B S T R A C T

Introduction: Amoebic encephalitis is a rare and potentially fatal central nervous system infection caused by free-living amoebae found in freshwater sources, such as lakes and rivers. There are two types of amoebic encephalitis, namely primary amoebic meningoencephalitis (PAM) and granulomatous amoebic encephalitis (GAE). Primary amoebic meningoencephalitis (PAM) is a disease typically caused by infection with *Naegleria fowleri*, a microscopic amoeba commonly referred to as a “brain-eating amoeba.” This infection destroys brain tissue, causing severe brain swelling and death in most cases. PAM is rare and usually occurs in otherwise healthy children, teens, and young adults. The initial symptoms of PAM are indistinguishable from those of bacterial meningitis, while the symptoms of GAE can mimic a brain abscess, encephalitis, or meningitis. These infections are almost uniformly fatal, with only a few reported survivors globally.

Materials and Methods: This review synthesized clinical, epidemiological, and laboratory findings from global literature on *N. fowleri* infections. Analysis encompassed the pathogen’s morphological life stages (trophozoite, flagellate, cyst), environmental drivers, mechanisms of neuroinvasion, and regional disease burdens across major affected countries (including the United States, Pakistan, Australia, and India). Diagnostic standards—such as direct cerebrospinal fluid (CSF) wet-mount microscopy, special staining (Giemsa/trichrome), molecular assays (PCR), and culture methods—were evaluated alongside current multidrug treatment regimens.

Results: *N. fowleri* flourishes in warm freshwater (up to 45.8°C). Infection typically occurs in healthy young individuals (median age 14; ~75% male) during water recreation. Upon entering the nasal cavity, trophozoites traverse the cribriform plate into the olfactory bulb, producing necrosis, micro-hemorrhages, and fatal cerebral edema. Globally, fewer than 500 cases have been documented, with only 11 confirmed survivors. While US cases remain low (0–8 annually), acute regional spikes have been observed, notably in Kerala, India, which reported 69 confirmed cases and 19 deaths late in 2025. CSF wet-mount identification of motile trophozoites and PCR assays remain primary diagnostic tools. Successful clinical management relies on prompt combination antimicrobial therapy—primarily intravenous/

intrathecal Amphotericin B, Miltefosine, azole antifungals, and targeted intracranial pressure management—initiated prior to extensive neurological destruction.

Discussion: The rising frequency of PAM in warming climates highlights its transition from an obscure tropical entity to a significant public health concern. Because the therapeutic window is extremely brief (frequently under 5 days from symptom onset), high clinical suspicion in endemic areas is vital to reduce initial misdiagnosis. Proposed clinical staging models (Nasal, Olfactory, and Meningoencephalitic phases) offer a framework for early intervention before irreversible CNS trauma occurs. Given the absence of targeted vaccines or definitive monotherapies, public health interventions—including public safety campaigns, nose-clip utilization during recreational swimming, and strict chlorination of municipal and recreational water sources—remain the primary line of defense.

Keywords: *Naegleria fowleri*; Primary Amoebic Meningoencephalitis; Brain-eating amoeba; Thermophilic amoeba; Kerala outbreak; Amphotericin B; Therapeutic hypothermia; Global health threat

Introduction

Free-living amoebae (FLA) are environmental protozoa commonly found in natural freshwater sources such as lakes, ponds, rivers, and hot springs. Among the various genera identified, four are primarily associated with human infections: *Naegleria* (specifically *Naegleria fowleri*), *Acanthamoeba* (multiple species), *Sappinia* (notably *Sappinia pedata*), and *Balamuthia* (specifically *Balamuthia mandrillaris*). Occasionally, other amoebae like *Vermamoeba vermiformis* (previously known as *Hartmannella*) have also been implicated in human disease.

These organisms are known for their neurotropic behavior, meaning they have an affinity for the central nervous system (CNS), often leading to severe brain infections such as meningoencephalitis. In addition to CNS infections, *Acanthamoeba* species can also cause ocular conditions like keratitis, particularly in contact lens users, as well as disseminated systemic infections in individuals with weakened immune systems.

Infections caused by free-living amoebae typically present in two major clinical forms:

- **Primary Amoebic Meningoencephalitis (PAM):** an acute and rapidly fatal condition primarily caused by *Naegleria fowleri*.
- **Granulomatous Amoebic Encephalitis (GAE):** a slower-progressing, chronic infection often associated with *Acanthamoeba* and *Balamuthia mandrillaris*, particularly in immunocompromised hosts.

Naegleria fowleri is responsible for causing Primary Amoebic Meningoencephalitis (PAM), a severe and rapidly progressing infection that affects the central nervous system (CNS). This disease is acute and often fatal, with symptoms typically appearing a few days after exposure to contaminated freshwater. Once symptoms begin, the infection usually leads to death within one to two weeks, primarily due to its swift progression and frequent delays in accurate diagnosis. Globally, only a small number of individuals—just 11 confirmed survivors—have recovered from *N. fowleri* infection, as documented in medical literature.

Species of *Naegleria* are commonly found in various natural environments, particularly in soil and freshwater or slightly salty water bodies such as lakes, ponds, and rivers. However, they do not survive in marine environments due to their sensitivity to high salinity, extreme pH levels, and dry conditions. In humans, *Naegleria* organisms are occasionally detected in the nasal passages and upper respiratory tract.

Notably, *N. fowleri* is thermophilic, meaning it thrives at elevated temperatures—surviving in environments as hot as 45.8°C. This heat tolerance makes it well-suited to infect warm-blooded hosts. Due to this characteristic, laboratory procedures for isolating *N. fowleri* from water samples typically involve incubation at approximately 45°C, which helps suppress the growth of other non-thermophilic amoebae. The organism is most frequently found in warm aquatic environments, including artificial lakes, hot springs, thermally polluted rivers, and other heated freshwater systems. In these ecosystems, it sustains itself by feeding on bacteria. Importantly,

N. fowleri is absent from saltwater bodies like oceans and seas. Infections are most commonly reported during the warmer months, particularly in the summer, when water temperatures favor the growth of amoebae.

Global Incidence And Cases

- **Rarity:** PAM is exceptionally rare. Since first description in the 1960s, fewer than 500 cases have been reported globally.
- **High Fatality Rate:** The mortality rate is over 97%. Only a handful of individuals worldwide have ever been reported to have survived the infection.
- **Affected Countries:** While cases have been reported in over 39 countries, the majority have been in the United States, Pakistan, Mexico, Australia, the Czech Republic, and India. These countries are more susceptible due to their warm climates, as the amoeba thrives in warm freshwater environments.
- **Rising Cases:** A slight increase in the number of reported cases annually in recent decades, which may

be linked to rising global temperatures and increased recreational water activities in warmer weather.

Demographics and Exposure

- **Age and Gender:** PAM most commonly affects healthy children and young adults, with a median age of 14 years. Approximately 75% of cases are in males.
- **Source of Infection:** The amoeba enters the body through the nose, typically during activities in warm freshwater like swimming, diving, or using unchlorinated water for nasal irrigation (e.g., neti pots). The amoeba then travels to the brain via the olfactory nerves.
- **Water Sources:** The most common sources of exposure are lakes, ponds, and reservoirs. Cases have also been linked to rivers, streams, hot springs, and improperly chlorinated swimming pools.

Cases by Region

- **India:** Cases have been reported in various parts of India, with a notable number of deaths in recent years, particularly in the state of Kerala. Public health authorities in Kerala have issued guidelines for diagnosis and management, and have had some success in increasing the survival rate through early detection and aggressive treatment.
- The state of Kerala is currently experiencing a notable increase in cases. As of late 2025, health authorities have reported 69 confirmed cases of PAM, resulting in 19 deaths this year. This is a considerable spike compared to typical global numbers and has prompted a public health alert.
- **United States:** The U.S. Centers for Disease Control and Prevention (CDC) reports a long-term average of

0 to 8 cases per year. Between 1962 and 2024, 167 reported cases have occurred in the United States, with only four survivors.

- **Pakistan:** Pakistan has the second-highest incidence of *Naegleria* infections globally. A significant number of deaths have been reported, particularly in the southern city of Karachi, where contaminated municipal water has been a major contributing factor.
- **Australia:** Australia was the first country to describe PAM cases in 1965. The country has reported a number of cases, with some recent occurrences linked to unusually high temperatures in specific regions.

Life Cycle of *N. fowleri*

The life cycle of *Naegleria fowleri* has three main stages: a trophozoite, a temporary flagellar stage, and a cyst. The trophozoite is the infective form responsible for human disease, while the other stages are critical for its survival and distribution in the environment.

Trophozoite Stage

The trophozoite is the active, feeding, and reproducing stage of the amoeba. It's the only stage that can reproduce asexually through binary fission. This is also the infectious form that causes disease in humans. In an infected person, trophozoites are found in the cerebrospinal fluid (CSF) and brain tissue.

Flagellate Stage

When environmental conditions are unfavorable, such as a lack of food, the trophozoite can transform into a temporary flagellate stage. In this form, the amoeba develops two flagella, allowing it to move quickly through water. This stage is non-feeding and serves as a means of distribution within water bodies. It can revert back to the trophozoite stage when conditions become more favorable.

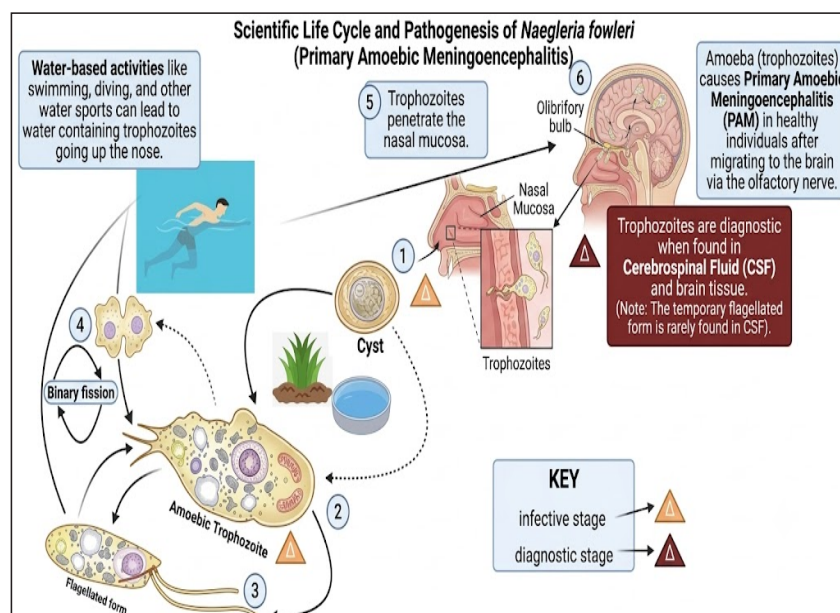


Table I. Life Cycle Stages of *Naegleria fowleri*

Stage	Environment / Trigger	Morphology & What Happens	Role in Infection / Survival
Trophozoite Stage (Active stage)	Favourable conditions: warm fresh or brackish water, abundant nutrients (bacteria)	Amoeboid form; actively feeding; size roughly 10–35 µm; single nucleus; moves by pseudopodia. Reproduces by binary fission.	This is the form that infects humans. If water enters the nose, trophozoites can travel along the olfactory nerve into CNS and cause disease.
Flagellate Stage (Temporary)	When water conditions change — e.g. fewer nutrients, or sudden environmental shifts (e.g. ionic concentrations)	Trophozoite transforms into a flagellated form (usually with two flagella) that swims. Non-feeding.	Allows for rapid dispersal in water. It's a temporary form, can revert to trophozoite when conditions improve. Rarely seen in human tissue.
Cyst Stage (Dormant / resistant)	Adverse or harsh conditions: cold, nutrient shortage, dryness	Rounded double-walled (or single-shelled, depending on source) cyst, about 7–15 µm, with a single nucleus. No feeding; resistant to environmental stress.	Enables the amoeba to survive long periods when external conditions are not good. When favorable conditions return (warmth, food), the cyst excysts into trophozoites. Not found in human brain tissue during acute infections.

Cyst Stage

In harsh conditions, like cold temperatures or a lack of nutrients, the flagellate form can transform into a double-walled cyst. This is a resistant, dormant stage that allows the amoeba to survive until the environment improves. Cysts are generally not found in clinical specimens from human infections because the disease progresses so rapidly that the patient dies before the amoeba has time to encyst within the host.

Clinical Stages of Primary Amoebic Meningoencephalitis (PAM)

Most individuals with Primary Amoebic Meningoencephalitis (PAM) are hospitalized while still in a state of consciousness, although often with significant neurological symptoms. Currently, there is no universally recognized clinical staging system for PAM. However, evidence from the few known survivors over the past six decades suggests that early detection and immediate initiation of appropriate treatment—especially during the early, pre-cerebral phase—can significantly improve the chances of survival.

To help clinicians recognize and act within this narrow window of opportunity, researchers at Aga Khan University Medical College have proposed a clinical staging model. This framework divides the infection into three distinct phases, based on the pathogen's progression and clinical manifestations:

Stage I – Nasal Phase (Pre-Cerebral Phase)

The infection begins when *Naegleria fowleri* enters the body through the nasal cavity, usually during exposure to contaminated warm freshwater. Water forced deep into the nasal passages allows the amoeba to contact the nasal mucosa. This stage often passes unnoticed, but it marks the entry point of the amoeba into the host.

Stage II – Olfactory Phase

If the organism advances beyond the nasal lining, it may reach the olfactory mucosa and eventually the olfactory bulb. This phase represents a transitional step before the amoeba penetrates the central nervous system. Symptoms at this stage may include alterations in the sense of smell (e.g., parosmia). Research, including studies using immunohistochemical techniques in animal models, has shown that *N. fowleri* can traverse the cribriform plate—a porous bone that separates the nasal cavity from the brain—and begin to replicate in the olfactory bulb. This triggers an early inflammatory response, often resulting in tissue damage such as necrosis, micro-hemorrhages, and the accumulation of inflammatory exudates.

Stage III – Meningoencephalitic Phase

Once the amoeba reaches the brain, it causes direct neural damage through both physical invasion and the secretion of toxic proteins. The resulting cellular debris, along with immune mediators such as cytokines, provokes a massive

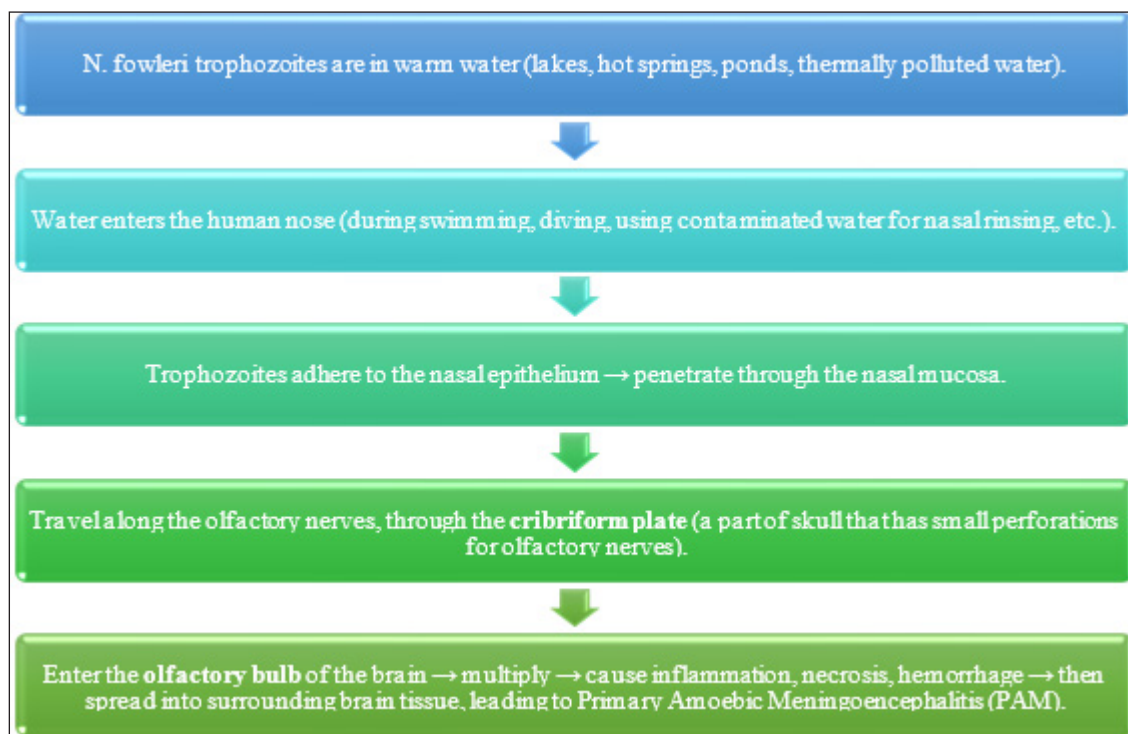


Figure 1. Transmission pathway of *Naegleria fowleri*

inflammatory response. This leads to rapid progression of meningoencephalitis, usually occurring within one to two days after the onset of the olfactory stage. Clinical deterioration is swift, with patients typically developing cerebral edema and brain herniation, which often result in death unless aggressive treatment is started very early.

Diagnosis Of Primary Amoebic Meningoencephalitis (Pam)

In cases of acute meningoencephalitis where bacterial and viral tests return negative, healthcare providers should strongly consider *Naegleria fowleri* as a potential cause, particularly in areas with recent or ongoing exposure risks. While a history of freshwater exposure (such as swimming in lakes or rivers) can support the diagnosis, it may not always be clearly reported by the patient or caregivers. In endemic areas such as Kerala, any patient with relevant environmental exposure should be considered a possible PAM case until proven otherwise.

Diagnostic Confirmation

The most immediate and reliable diagnostic method involves examining a freshly collected cerebrospinal fluid (CSF) sample under a microscope. A wet mount may reveal actively motile *N. fowleri* trophozoites. Using a

phase-contrast microscope can enhance visibility of these organisms. However, it essential to note that trophozoites

can lose their motility quickly and resemble white blood cells, making identification more challenging.

Staining Techniques

Special stains such as Giemsa or trichrome can help distinguish *N. fowleri* by highlighting key morphological features. The trophozoites are typically 10–25 microns in size, possessing a single nucleus with a centrally placed nucleolus and lacking peripheral chromatin—features that are distinctive when properly stained.

Molecular Diagnosis

Polymerase chain reaction (PCR) testing of CSF is a valuable tool for detecting the DNA of *N. fowleri* and other free-living amoebae. This method provides rapid and specific confirmation. Additionally, culturing can be attempted using non-nutrient agar plates layered with enteric bacteria like *E. coli* or *Klebsiella*, which serve as a food source for the amoeba.

Other Methods

Serological testing is not reliable for diagnosing PAM, as antibody development typically occurs too late in the disease process to be useful. According to guidance from the Centers for Disease Control and Prevention (CDC), CSF samples should be examined as soon as possible—fresh, unfrozen, and not refrigerated—to increase the chances of detecting live amoebae. If trophozoites are observed, PCR should be used to confirm the diagnosis.

Imaging Studies

Radiological findings on CT or MRI scans are usually non-specific. Some findings may include brain swelling (edema), inflammation of the basal meninges, hydrocephalus, or localized areas of infarction. Brain lesions often appear in the orbitofrontal cortex, temporal lobes, cerebellum, base of the brain, or upper spinal cord.

Histopathology

On autopsy or biopsy, typical findings include suppurative inflammation along the leptomeninges, along with extensive brain tissue necrosis and hemorrhaging. Brain samples may be stained with immunofluorescent antibodies specific to *N. fowleri* for definitive identification.

Differential Diagnosis

PAM can closely resemble acute bacterial meningitis in its early clinical presentation and CSF findings, which often leads to patients being initially treated with antibiotics. Distinguishing between the two may rely on recognizing epidemiological clues, such as recent swimming in warm freshwater. Due to overlapping symptoms, misdiagnosis is common, underscoring the need for awareness in at-risk regions.

Management & Treatment

Primary Amoebic Meningoencephalitis (PAM) is a rapidly progressing and typically fatal infection caused by the free-living amoeba *Naegleria fowleri*. Due to its aggressive nature, early recognition and immediate initiation of treatment are critical for any chance of survival. Although there is no universally standardized treatment protocol, successful cases reported in medical literature provide valuable insight into effective therapeutic strategies.

General Treatment Approach

Because of PAM's rapid progression, treatment must begin as soon as the disease is suspected—even before laboratory confirmation. The goal is to:

- Halt the amoeba's replication.
- Reduce inflammation in the brain.
- Prevent or manage complications like brain edema and seizures.

A multidrug regimen is often used, combining antiparasitic, antifungal, antibiotic, and anti-inflammatory agents.

Core Antimicrobial Agents Used

Amphotericin B

- **Mechanism:** Binds to ergosterol in the amoeba's cell membrane, causing cell death.
- **Use:** Considered the cornerstone of PAM treatment.

Administration

- Intravenous (IV) form for systemic action.
- Intrathecal (IT) or intraventricular administration (directly into the CSF) may be used in severe cases to ensure adequate CNS penetration.
- **Limitations:** High toxicity; side effects include nephrotoxicity and electrolyte imbalance.

Miltefosine

- **Mechanism:** Originally developed as an anti-leishmanial drug, it disrupts membrane integrity and mitochondrial function in amoebae.
- **Use:** Shown promising results in some PAM survivors.

Advantages

- Oral administration.
- Better CNS penetration compared to some other agents.
- **Status:** Not yet widely available everywhere, but has been increasingly used in experimental and emergency protocols.

Azole Antifungals (e.g., Fluconazole, Ketoconazole, Posaconazole)

- **Mechanism:** Inhibit sterol synthesis in the amoeba's cell membrane.
- **Use:** Often added as adjunctive therapy.
- **Fluconazole** is commonly preferred for its CNS penetration.

Rifampicin

- **Mechanism:** Bacterial RNA polymerase inhibitor; believed to enhance efficacy when used in combination with other drugs.
- **Use:** Often included in combination regimens for potential synergistic effects.

Azithromycin

- **Mechanism:** Inhibits protein synthesis in some protozoa.
- **Use:** Has shown activity against *N. fowleri* in laboratory studies; sometimes added to treatment protocols.
- Supportive and Adjunctive Treatments

Management of Cerebral Edema

- Mannitol and hypertonic saline may be used to reduce intracranial pressure.
- Mechanical ventilation is often required in critically ill patients.
- Monitoring for signs of herniation or increased intracranial pressure is crucial.

Steroids (e.g., Dexamethasone)

- Used to control inflammation and cerebral edema, although their benefit is still debated.

Therapeutic Hypothermia

Lowering body temperature (induced hypothermia) has been tried in some cases to reduce cerebral metabolic demand and inflammation.

Experimental and Novel Approaches

- **Immunotherapy:** Some research has explored the use of immune modulators to enhance the host's response to the amoeba.
- **Nanomedicine and Drug Delivery Systems:** Novel strategies to improve CNS drug delivery are under investigation.
- **High-throughput screening** of drug libraries is ongoing to identify more potent anti-amoebic compounds.

Challenges in Treatment

- **Delayed Diagnosis:** Many patients are initially misdiagnosed with bacterial or viral meningitis.
- **Poor CNS Penetration:** Some drugs fail to reach therapeutic concentrations in brain tissue.
- **Rapid Disease Progression:** The time window for effective treatment is very narrow—often less than 5 days from symptom onset.
- **Limited Availability of Drugs:** Miltefosine and intrathecal amphotericin B are not readily accessible in many regions.

Notable Survivor Cases

A few documented survivors of PAM have received early, aggressive combination therapy, including:

- Intravenous and intrathecal **Amphotericin B**.
- **Miltefosine** initiated early.
- Supportive care in an **intensive care unit (ICU)**.
- **Therapeutic hypothermia** to manage brain swelling. These cases highlight the importance of high clinical suspicion and rapid, multimodal treatment.

Public Health and Prophylaxis

- **No vaccine or prophylactic treatment** currently exists for PAM.
- **Preventive strategies** focus on public education, especially in endemic regions, emphasizing:
- Avoiding warm freshwater activities in summer.
- Using nose clips during water exposure.
- Ensuring proper chlorination of swimming pools and recreational water sources.

Prevention of Primary Amoebic Meningoencephalitis (PAM)

Primary Amoebic Meningoencephalitis (PAM) is a rare but nearly always fatal brain infection caused by the thermophilic amoeba *Naegleria fowleri*. Since the infection progresses rapidly and treatment is often ineffective unless

initiated very early, prevention remains the most effective strategy for combating this disease.

Public Awareness and Education

Raising awareness in communities—especially in areas where the disease is endemic—is essential. Most cases occur in children and young adults who engage in water-based recreational activities. Educating the public about the risk of *N. fowleri* in warm freshwater bodies during hot weather is a key component of prevention.

Awareness efforts should include:

- Informational signage at lakes, rivers, and hot springs during the summer months.
- School-based education in affected regions.
- Public health campaigns during high-risk seasons.

Avoiding High-Risk Water Exposure

The main route of infection is through the **nasal cavity**, especially when water is forcefully inhaled into the nose. Preventing water from entering the nose during aquatic activities can significantly reduce the risk.

Recommendations include:

- Avoid swimming or diving in warm, stagnant freshwater during hot weather.
- Refrain from jumping into freshwater lakes, rivers, and hot springs where *N. fowleri* may thrive.
- Do not disturb bottom sediments in shallow, warm freshwater.

Use of Protective Equipment

When swimming or engaging in water sports in potentially contaminated water:

- Use nose clips or hold the nose shut to prevent water from entering the nasal passages.
- Avoid submerging the head under water.
- Do not allow children to play in warm freshwater that may go up the nose.

Safe Water Practices at Home

N. fowleri has also been isolated from untreated tap water in rare cases, particularly in areas with poorly maintained municipal water systems.

Precautions at home include:

Use only sterile or distilled water for:

- Nasal irrigation (e.g., neti pots).
- Sinus rinsing.
- Boil tap water for at least 1 minute (or 3 minutes at high altitudes) and allow it to cool before using it for nasal cleansing.
- Clean and disinfect neti pots or similar devices after each use.

Water Treatment and Infrastructure Maintenance

Maintaining safe and properly chlorinated public water supplies is crucial. *N. fowleri* is sensitive to chlorine and does not survive in properly treated water systems.

Water treatment guidelines include:

- Regular monitoring of chlorine levels in municipal water systems and swimming pools.
- Ensure free chlorine residuals of at least 0.5 mg/L in recreational water facilities.
- Routine maintenance and cleaning of water storage tanks, pipes, and swimming pools.

Environmental and Seasonal Monitoring

Authorities in high-risk regions can implement seasonal surveillance of freshwater bodies to detect the presence of *N. fowleri*, particularly during periods of high temperatures when the risk is highest.

- Restrict access to contaminated recreational water bodies.
- Alert the public when environmental conditions are favorable for amoeba growth (e.g., prolonged heatwaves, low water flow, or high-water temperatures).

Personal Hygiene

- After swimming in freshwater, blow the nose forcefully to help expel any water that may have entered.
- Avoid swimming if you have a nasal injury, open wounds, or recent sinus surgery, which may increase susceptibility.

Conclusion

Primary Amoebic Meningoencephalitis (PAM) caused by *Naegleria fowleri* remains one of the most devastating infections of the central nervous system, with an almost universal fatality rate. Although rare, its rising incidence in warmer climates and regions with inadequate water safety measures underscores its growing significance as a public health threat. The disease's rapid progression, diagnostic challenges, and limited therapeutic options highlight the urgent need for heightened clinical awareness, early detection, and aggressive multimodal treatment strategies.

Survivor case reports demonstrate that timely intervention with amphotericin B, miltefosine, and supportive therapies such as therapeutic hypothermia can improve outcomes, but the therapeutic window is extremely narrow. In the absence of vaccines or definitive prophylaxis, prevention through public education, safe water practices, and strict chlorination of municipal and recreational water supplies remains the most effective strategy. Strengthening surveillance in endemic regions, coupled with global collaboration, will be essential to mitigate the impact of PAM and reduce mortality.

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