

Beyond Brain-Eating Amoebas: Current Insights into *Naegleria fowleri* Identification, Prevalence, and Treatment

Ijaz Usman Ali¹ , Muhammad Shoaib Akhtar¹ , Hina Naz² , Ahmad Waheed^{2*} , Ijaz Ahmed¹, Jawad Ahmad¹, Inam Ullah¹, Muhammad Mumtaz Tahir¹, Feruza Ravshanovna Zokirova³ 

¹Department of Microbiology and Molecular Genetics, Faculty of Life Sciences, University of Okara, Okara 56130, Pakistan

²Department of Zoology, Faculty of Life Sciences, University of Okara, Okara 56130, Pakistan

³Department of Information Technologies, Tashkent State Technical University, Tashkent, Uzbekistan

*Corresponding author: wahmad09@yahoo.com

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Abstract

Naegleria fowleri, commonly known as the “brain-eating amoeba,” is an opportunistic, free-living protozoan responsible for primary amoebic meningoencephalitis (PAM), a rare but almost invariably fatal infection of the central nervous system. This thermophilic amoeba thrives in warm freshwater environments such as lakes, hot springs, and poorly maintained swimming pools. It can survive under high temperatures, making it more prevalent in regions with warm climates and developed countries, including Australia, Europe, and the United States. This review summarizes current evidence on the global prevalence, clinical presentation, diagnostic challenges, and treatment strategies related to *N. fowleri* infections. Epidemiological data indicate that approximately 26.4% of global freshwater sources contain *Naegleria* species, with the highest prevalence recorded in the Americas at 33.2%. Infected individuals typically present with acute symptoms such as severe headache, high fever (101–105°F), neck stiffness, seizures, altered mental status, and coma, with disease progression often resulting in death within one to two weeks of symptom onset. Despite advances in supportive care and antimicrobial therapy, the case fatality rate remains over 90%. Conventional diagnostic methods include microscopy, culture, serology, imaging, and molecular techniques such as real-time PCR; however, delays in diagnosis often hamper timely treatment. Therapeutic regimens traditionally involve a combination of antifungal and antimicrobial agents, including amphotericin B, azoles, azithromycin, and miltefosine. Although amphotericin B is considered the gold standard due to its potent amoebicidal activity at concentrations as low as 0.01 µg/ml, its poor solubility and high toxicity can cause significant adverse effects such as nephrotoxicity, hematologic complications, and systemic symptoms like headache, vomiting, and fever. Additionally, in vitro studies have shown that *N. fowleri* may develop resistance to miltefosine at concentrations up to 40 µg/ml. This review underscores the critical need for early and accurate diagnostic tools, safer and more effective therapeutic alternatives, and greater public awareness to prevent exposure and improve patient survival. Further research is urgently required to develop novel treatment options and reduce the devastating impact of this neglected but deadly pathogen.

Keywords: Meningoencephalitis, Molecular Diagnosis, *Naegleria fowleri*, Miltefosine, Amphotericin B.

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1. Introduction

Naegleria fowleri, commonly referred to as the “brain-eating amoeba,” is a thermophilic, free-living protozoan that causes primary amoebic meningoencephalitis (PAM), a rare but almost universally fatal infection of the central

nervous system (CNS) (Datta, 2024; Kurup et al., 2022; Sriram & Chandra, 2024). This amoeba thrives in warm freshwater environments such as lakes, hot springs, rivers, inadequately chlorinated swimming pools, and poorly maintained water distribution systems (Shirsath et al., 2024). Although often perceived as geographically limited, *N.*

fowleri has been reported worldwide, including in the Americas, Europe, Asia, Africa, and Australia (Alanazi et al., 2025). A systematic review by Gharpure et al. (2020) documented cases in diverse climates, demonstrating that rising global temperatures may expand its geographic range, posing new risks in previously unaffected areas. Despite its environmental ubiquity, human infections remain rare, with fewer than 500 reported cases globally (Capewell et al., 2015). However, the high fatality rate, rapid disease progression, and lack of effective therapeutic options have made PAM a subject of growing concern (Mungroo et al., 2019). Most infections occur during recreational water activities in warm months when water temperatures exceed 25°C (Stahl & Olson, 2020).

While numerous studies have described the organism's biology and global prevalence, inconsistencies in surveillance methods and underreporting hinder accurate estimation of its true distribution. There is also insufficient comparative analysis of diagnostic and therapeutic practices across regions, which limits our ability to identify critical gaps in prevention and treatment. This review aims to synthesize current knowledge of *N. fowleri* biology, prevalence, clinical features, diagnostic strategies, and therapeutic challenges, highlighting unresolved questions and emerging directions for future research.

2. Diagnosis of Primary Amoebic Meningoencephalitis

Early and accurate diagnosis of *Naegleria fowleri* infection is critical due to the rapid progression and high fatality of PAM (Phung et al., 2025). However, diagnosis remains challenging, as initial clinical symptoms often mimic bacterial or viral meningitis, leading to misdiagnosis or delayed treatment (Siddiqui et al., 2025). Several diagnostic methods have been developed, each with distinct advantages and limitations.

2.1. RT-PCR

RT-PCR for the recognition of *N. fowleri* proved its sensitivity and specificity; thus, it is a useful substitute for cultivation and microscopy (Saber et al., 2020). But there are some disadvantages; such as being expensive (RFLP), nonetheless, it overcomes the late and retroactive diagnosis (ELISA), time-consuming (cultivation), or incomplete results (flagellation test) for the diagnosis of both environmental and analytic samples (Madarova et al., 2010). One of the fundamental benefits is the probability of separating DNA from specimens without preceding culture (Maclean et al., 2004). Also, PCR helps the identification of remaining spp. of the *Naegleria* genus (Madarova et al., 2010). Such particular

tests for *N. fowleri* should be endorsed to verify suspected contagious mediums in analytic samples (Madarova et al., 2010). Nevertheless, their use is often limited by availability in resource-limited settings and the need for specialized equipment and trained personnel.

2.2. Imaging Methods

Magnetic Resonance Imaging (MRI) shows abrasions, or Computed Tomography (CT) scans the abrasions, but these are general overviews (Kidney & Kim, 1998; Schumacher et al., 1995; Singh et al., 2006). On the other hand, CT scans reveal the eradication of the cisterns encircling the subarachnoid space and the midbrain (Martinez, 2019). MRI or CT scans can help identify brain edema and inflammation but do not specifically differentiate PAM from other forms of meningoencephalitis (Mahajan & Mahajan, 2024). Thus, imaging primarily supports differential diagnosis and treatment planning rather than confirming *N. fowleri* infection.

2.3. Serology

Antibodies of *Naegleria* spp. had been detected in serologically active people (Marciano-Cabral & Cabral, 2007; Marciano-Cabral et al., 1987). Serological tests are not always fruitful because PAM is a swift disease. Usually, no increase is recorded in antibody titers, except within victims that were effectively examined and recovered from the inflammation (Vargas-Zepeda et al., 2005). Moreover, serological tests are generally of limited clinical value for PAM diagnosis, as they often fail to detect infection in the acute phase when rapid treatment decisions are needed (Christopher-Hennings et al., 2019).

2.4. Culture Methods

Biopsied brain tissues or cerebrospinal fluid (CSF) should be transferred to the diagnostic laboratory and kept at room temperature. This material can be implanted onto the micropropagation cells and cultivated at 37 °C in the existence of the antiseptics, e.g., streptomycin and penicillin (Mungroo et al., 2020). The available amoeba will replicate and damage the monolayers in 24-48 hours (Schuster, 2002). Autopsy tissue can also be spotted on 1.5% non-nutrient agar covered with a film of bacteria (*E. coli*) (Martinez, 1985; Martínez et al., 1980; Martinez & Visvesvara, 1991; Schuster, 2002). The amoebae will develop from the tissue, absorb the bacteria, and replicate (Hundt & Ruffolo, 2005). Using an inverted light microscope, amoeba can be observed on agar in the form of flagellates (Martinez, 1985) as shown in Fig. 1.



Fig. 1. Flagellated form of *N. fowleri* under inverted light microscope. Source: CDC (2024b)

These techniques typically using non-nutrient agar with an *Escherichia coli* layer, can confirm viability and support species identification (Değerli et al., 2020). However, culture is time-consuming and may not provide timely results for urgent clinical management.

2.5. Microscopic Methods

An antemortem examination is very uncommon, but when cerebrospinal fluid pressure is low, a spinal tap can be achieved (Martinez & Visvesvara, 1991). The cerebrospinal fluid is slightly hemorrhagic and cloudy, with elevated cellularity and consisting mostly of neutrophils (Di Terlizzi & Platt, 2009). CSF is described by elevated protein and low glucose (Seehusen et al., 2003). The direct microscopic examination of cerebrospinal fluid as a wet mount is the technique of choice for PAM examination (Martinez & Visvesvara, 1991). CSF consists of moveable amoebae, which can be identified by light microscopic examination (Martínez et al., 1980; Martinez & Visvesvara, 1991, 1997). When amoebae are implanted in water, they can transform into swimming flagellates (Fig. 1); *N. fowleri* was distinguished from other brain and spinal cord infections causing free-living amoeba (FLA). If available in cerebrospinal fluid, amoebae can be recognized by staining fixed preparations with Wright's or Giemsa (Fig. 2). However, gram stain is utilized in scientific labs for the identification

of bacteria in cerebrospinal fluid, but gram stain is not functional for the examination of amoebae (Martinez, 1985; Martínez et al., 1980; Martinez & Visvesvara, 1991; Trabelsi et al., 2012).

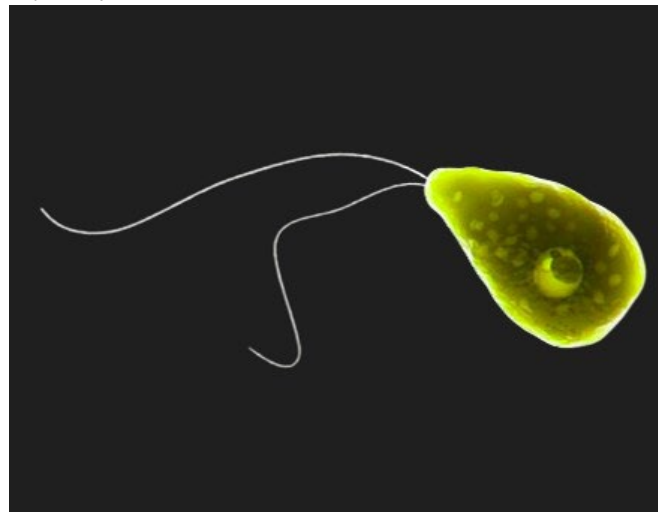


Fig. 2. Wright's or Giemsa staining to identify *N. fowleri*. Source: CDC (2024a)

Although microscopy is quick and inexpensive, its accuracy heavily depends on sample handling, the examiner's expertise, and parasite concentration in the CSF.

3. Prevalence and Epidemiology of *N. fowleri*

The global distribution of *Naegleria fowleri* is more widespread than commonly recognized (Gabriel et al., 2019; Maciver et al., 2020; Reyes-Batlle et al., 2019; Saberi et al., 2020; Siddiqui & Khan, 2014; Trabelsi et al., 2012), yet the true burden of human infections remains underestimated due to underreporting, limited surveillance, and misdiagnosis (Alanazi et al., 2025). A meta-analysis by Saberi et al. (2020) found that *Naegleria* species are present in approximately 26–30% of freshwater bodies worldwide, with the highest detection rates reported in North and South America (up to 33%) and increasing reports from Asia and Africa.

Despite this environmental prevalence, PAM remains a rare disease, with fewer than 10 reported cases annually in the United States and sporadic cases elsewhere (Diaz, 2012). This apparent inconsistency can be partly explained by the pathogen's specific transmission route: infection occurs when contaminated water forcefully enters the nasal passages during activities such as swimming or diving, allowing the amoeba to migrate along the olfactory nerves to the brain (Capewell et al., 2015). Routine ingestion of contaminated water does not cause infection.

Climatic changes and urbanization are likely to expand the geographical range of *N. fowleri* by warming freshwater habitats and affecting water treatment infrastructure (Stahl et al., 2025). Notably, isolated reports of *N. fowleri* in non-traditional habitats, including poorly chlorinated tap water and geothermal power plant runoff, suggest the need for robust environmental monitoring and maintenance of water quality standards (Bartrand et al., 2014).

Current surveillance data remain fragmented, with most studies relying on environmental sampling without standardized protocols. Additionally, reliable data from developing countries is scarce due to limited diagnostic

capacity and reporting systems. Therefore, improving systematic surveillance, especially in underreported regions, is essential to accurately map the risk of exposure and guide public health interventions.

This synthesis highlights the need for harmonized monitoring strategies, incorporation of molecular detection in routine water testing, and heightened clinical awareness in both endemic and emerging regions. Table 1 shows a comprehensive review of the previous studies conducted on the Prevalence of *Naegleria spp.* in origins of water across various countries.

Table 1. Prevalence of *Naegleria spp.* in various countries' water sources. All the samples were environmental samples.

Country	Prevalence	Year	Methods	Sampling Year	Sample Number	References
Taiwan	14.5%	2010	PCR	2007–2009	62	(Huang & Hsu, 2010)
USA	26.67%	2010	PCR	2006–2008	30	(Laseke et al., 2010)
Italy	72.00%	2017	PCR	2013–2015	25	(Di Filippo et al., 2017)
South Africa	1.00%	2017	PCR	2016	100	(Muchesa et al., 2017)
Spain	10.00%	2017	PCR	2016	10	(Reyes-Batlle et al., 2017)
Pakistan	25.00%	2017	PCR	2016–2017	120	(Tanveer et al., 2017)
Egypt	26.00%	2018	PCR	2016–2017	102	(Abd El Wahab et al., 2018)
Philippines	26.00%	2019	PCR	2017–2018	54	(Milanez et al., 2019)
Egypt	23.79%	2023	PCR	2021–2022	165	(Elseadawy et al., 2023)
France	16.51%	2011	Nested PCR	2009–2010	103	(Ahmad et al., 2011)
Egypt	38.02%	2014	Morphology	2012–2013	250	(Al-Herrawy et al., 2014)
Egypt	0.89%	2014	Morphology	2012	112	(Khalifa et al., 2014)
USA	30.14%	2003	ELISA	2000–2001	71	(Reveiller et al., 2003)
USA	66.67%	2013	qPCR	2011–2012	9	(Painter et al., 2013)
Turkey	2.7%	2021	qPCR	2018–2020	111	(Aykur & Dagci, 2021)
Korean	11.54%	2018	Real-time PCR	2016–2017	52	(Kim et al., 2018)
Thailand	1.47%	2004	Zymogram patterns	2003	68	(Tiewcharoen et al., 2004)

Malaysia	29.00%	2019	Plating assays/PCR	2017–2018	45	(Gabriel et al., 2019)
Mexico	7.00%	2014	Morphology/Plating assays	2013	43	(Bonilla-Lemus et al., 2014)
Spain	14.28%	2019	Morphology/PCR	2018	21	(Reyes-Batlle et al., 2019)
Iran	54.00%	2017	Morphology/PCR	2015	50	(Latifi et al., 2017)
Thailand	9.00%	2018	Morphology/PCR	2016–2017	33	(Tiewcharoen et al., 2018)
Sri Lanka	23.07%	2020	Plating assays/PCR	2019	78	(Gunarathna et al., 2021)
India	20.7%	2022	Microscopy/NA/PCR	2020–2021	29	(Krishnamoorti et al., 2022)

4. Prevalence of PAM in Pakistan

The accessible data revealed that the number of died people due to PAM has enhanced in few previous years. Despite that PAM first record was in 2008, till 2018, 13 deaths were recorded in Pakistan. Fifteen deaths were recorded in 2019 until October (Tabassum et al., 2022). There were no deaths recorded in 2020. Six deaths were recorded in 2021. However, first death due to PAM for the year 2022 was recorded on 2nd of May. The victim was from Kemari (Karachi) who is 59-year-old. Four cases of PAM were recorded until July 1, 2022. By the reports of to Dr. Bahoto, Director-General of the Sindh Health Department, all 4 victims had no records of entertaining water practices, and they were probably affected by household water supply (Tabassum et al., 2022). People from 26–45 years old were mostly affected by PAM in Pakistan (Naqvi et al., 2016).

In the summer, PAM cases are generally reported from April to September (Naqvi et al., 2016). Recently, it was revealed that samples of water were taken from several zones all over Karachi, along with two major sources and the zones provided by these distribution systems. Specimens of water were sent to identify *N. fowleri* via culture and PCR, which came back positive (Ghanchi, 2018). This is astonishing, given that the water in Karachi is frequently saline, and amoebas are not able to develop in saline water, revealing that the *N. fowleri* strain experienced in Pakistan is definite from those recorded worldwide, or it may have developed a defiance to the briny ecosystem (Ali et al., 2020).

Moreover, a recent survey analysis by Aurongzeb et al. (2025) reported that PCR analysis using ITS- and Naegl-primers showed that *N. fowleri* was present in 11 out of 39 environmental samples (tap water) from Karachi. The main

areas where *N. fowleri* identification was done included Lyari and Golimar areas. So, Aurongzeb et al. (2025) suggested that the presence of coliforms, high temperatures, and inadequate chlorination may all contribute to the presence of *N. fowleri* in these areas of Pakistan.

5.1 Treatment of PAM due *Naegleria fowleri*

Recently, The most utilized drug for the treatment of *N. fowleri* infections is Amphotericin B (AmB), an antifungal agent that kills amoebas by activating an apoptosis-like programmed cell death (PCD) (Cardenas-Zuniga et al., 2017). Formerly, the intrathecal or interveinal regime of AmB alone or conjugated with other medicines including Azithromycin (AZM), Rifampin (RIF), and Fluconazole (FCZ) has revealed some effectiveness in eradicating the amoeba when given in primary phase of the disease (Bellini et al., 2018; Grace et al., 2015). Furthermore, Miltefosine (MLT), an alkylphosphocholine compound utilized initially to control leishmania infections and cancer of chest in women (Verweij et al., 1992). It was thought to be a rare therapeutic drug used for the treatment of PAM until it was effectively treated; a 12-year-old child who withstand the infection with a complete neurological rehabilitation (Heggie & Kupper, 2017; Rice et al., 2020). This treatment protocol was later utilized on two distinct victims of PAM, where one of them got through with a poor neurological condition and the other could not survive (Cope et al., 2016). Though MLT is an assuring drug used for the cure of PAM, it does not guarantee complete rehabilitation from the infection (Cope et al., 2016).

5.2. Amphotericin B

There have been zero clinical trials to date that examine the potency of one treatment administration over another due to the rarity of *N. fowleri* infections in humans (Kim, Lee, et al., 2008). Most of the information concerning medication effectiveness was established through either in vitro studies or case reports (Kim, Lee, et al., 2008). The 0.01 µg/ml of amphotericin B is considered the minimum amoebicidal concentration utilized to control *N. fowleri* (Goswick & Brenner, 2003; Kim, Jung, et al., 2008). On the other hand, in vitro studies revealed that 0.1 µg/ml concentration of amphotericin B was required to decrease over 90% of *N. fowleri* development (Goswick & Brenner, 2003), while 0.39 µg/ml was required for the complete suppression of amoeba reproduction (Barnett et al., 1996). The suggested period of therapy is 10 days when amphotericin B is utilized for the medication of *N. fowleri* (Barnett et al., 1996; Hannisch & Hallagan, 1997). Amphotericin B (AmB) is not soluble in water (Torrado et al., 2008), therefore, it is very toxic and causes hematopoietic effects, electrolyte imbalances, renal toxicity, and other clinical symptoms like headache, nausea, chills, fever, and vomiting (Laniado-Laborin & Cabrales-Vargas, 2009). These complications clarify the importance of finding a safer and more effective alternative that can be used against *N. fowleri* (Cardenas-Zuniga et al., 2017; Debnath et al., 2012).

5.3. Miltefosine

Two victims of diseases caused by *N. fowleri* recovered after being cured with miltefosine in 2013 (Capewell et al., 2015). It is made up of phosphate and lipids (Dorlo et al., 2012) which are also attached to choline (Fig. 3). The detailed structures of miltefosine are amphiphile in nature, containing an aliphatic tail and a head region consisting of phosphate and choline (Grace et al., 2015). The mechanism of miltefosine action was proved as an inhibitory effect against protein kinase B (Dorlo et al., 2012).

Treatment of primary amoebic meningoencephalitis caused by *N. fowleri* is a challenging task because the disease is not only uncommon, but also has a low morbidity and high mortality rates (Visvesvara, 2013). Some of the antifungal drugs clinically approved can be utilized to control infections due to *Naegleria* species, e.g., Fluconazole, Azithromycin, and Rifampin (Grace et al., 2015). This is because the sterol biosynthesis pathway in infectious fungi is same in free-living amoeba (Debnath et al., 2017).

6. Recent Therapeutic Approaches and Emerging Treatments

Recent research has focused on drug repositioning, nanoparticle delivery systems, and combination therapies

to enhance efficacy and reduce toxicity (Siddiqui et al., 2024; Siddiqui et al., 2025). Several in-vitro and in-vivo studies have shown that repurposed FDA-approved drugs, such as statins, antipsychotics, and anticancer agents, may exhibit anti-amoebic activity, providing promising leads for combination regimens (Elsheikha et al., 2020).

Nanoparticle-based formulations of amphotericin B and other drugs have been explored to improve blood–brain barrier penetration, increase bioavailability, and reduce systemic toxicity (Siddiqui et al., 2024). For example, liposomal amphotericin B has demonstrated enhanced efficacy in experimental models, although human data remain limited (Adler-Moore et al., 2019). Other experimental approaches include silver and gold nanoparticles, which have shown amoebicidal effects in vitro (Anwar et al., 2019).

7. Conclusion

Primary amoebic meningoencephalitis caused by *Naegleria fowleri* remains one of the most challenging infectious diseases due to its rarity, rapid progression, and extremely high fatality rate despite aggressive treatment. Although the environmental presence of *N. fowleri* is well established across diverse freshwater sources globally, accurate assessment of human risk is still hampered by inconsistent surveillance, limited diagnostic awareness, and underreporting, especially in low- and middle-income countries. Current diagnostic methods, while advanced in laboratory settings, are not always practical or widely accessible for early clinical detection. Similarly, despite amphotericin B and miltefosine offering some therapeutic promise, their limitations in terms of toxicity, resistance, and delivery to the central nervous system continue to hinder treatment success. To meaningfully reduce the burden of PAM, several areas require urgent attention. First, robust and harmonized surveillance systems should be developed, particularly in regions with inadequate water treatment infrastructure and cultural practices that may increase nasal exposure. Second, clinical diagnostic protocols should integrate rapid, point-of-care molecular tools alongside improved training for healthcare professionals to recognize this rare disease early. Future therapeutic strategies must prioritize the development and clinical validation of new compounds and delivery systems, including nanoparticle-based formulations and drug repositioning approaches, to overcome the barriers posed by the blood–brain barrier and drug toxicity. Collaboration across microbiology, nanotechnology, and pharmaceutical research is essential to translate promising in vitro findings into viable treatments. Lastly, coordinated public health campaigns focused on risk reduction (like promoting safe recreational

water use and proper chlorination) are vital for community-level prevention. By addressing these critical research and implementation gaps, the devastating outcomes associated with *N. fowleri* infections may be significantly mitigated, transforming a neglected and often fatal condition into a more preventable and treatable disease.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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