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REVIEW

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Naegleria fowleri: emerging therapies and translational challenges

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ABSTRACT

Introduction: *Naegleria fowleri* is a rare but fatal free-living ameba with > 97% mortality rate. Despite advances in clinical and scientific understanding, therapeutic options remain limited, and diagnosis is often delayed, presenting significant public health challenges.

Areas covered: We reviewed recent literature from the last decade, using Google Scholar and PubMed on *N. fowleri* treatment, emerging drug candidates, repurposed therapeutics, and innovative delivery strategies. Advancements in drug screening are highlighted, unveiling novel therapeutic targets and mechanisms of action. Additionally, the role of climate change and environmental factors in geographic expansion and increased incidence of infections is explored, posing a growing public health risk.

Expert opinion: Effective management of *N. fowleri* infections hinges on early detection and addressing research gaps, particularly in understanding transmission/disease mechanisms. Recent advances in therapeutics, diagnostics, and water treatment to reduce environmental contamination by *N. fowleri* show promise for lowering infection risk and improving outcomes for primary amebic meningoencephalitis. Collaboration among academic institutions, pharmaceutical companies, and water industries is essential, with research advancing treatments and vaccines, and water industries contributing by reducing environmental contamination/human exposure to *N. fowleri*. A combination of treatment strategies and stringent surveillance will be crucial to limit future outbreaks and improve patient prognosis.

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Naegleria fowleri; climate change; free-living amebae; novel therapeutics; drug discovery

1. Introduction

Naegleria fowleri is a thermophilic, free-living ameba commonly found in warm freshwater environments worldwide. It is the causative agent of primary amebic meningoencephalitis (PAM), a rare but nearly always fatal infection of the central nervous system (CNS) [1,2]. Infection occurs when *N. fowleri* trophozoites enter the nasal passages during exposure to contaminated water, commonly through swimming, ritual ablution, or nasal irrigation [3]. The amebae adhere to the nasal mucosa, traverse the olfactory neuroepithelium, and migrate via the olfactory nerve to the brain. There, they provoke acute inflammation and rapid tissue destruction, leading to severe CNS damage and, in most cases, death within a week of symptom onset [4]. The disease typically progresses in two stages: the early phase is characterized by headache, fever, nausea, and vomiting, while the later stage includes more severe neurological symptoms such as stiff neck, seizures, confusion, and coma [5].

Currently, there is no consistently effective treatment for PAM, and the case fatality rate exceeds 97% [6]. Standard Centers for Disease Control and Prevention (CDC)-recommended therapy includes a combination of drugs such as amphotericin B, miltefosine, fluconazole, rifampin, azithromycin, and dexamethasone [7,8]. However, these treatments are associated with substantial limitations, including high toxicity, particularly nephrotoxicity from amphotericin B, and poor blood–brain barrier penetration, which impedes effective CNS delivery [9–12]. While this multi-drug regimen may target *N. fowleri* through different mechanisms, the potential for pharmacological interactions should be considered. The combination of nephrotoxic agents such as amphotericin B with other hepatotoxic or nephrotoxic drugs may increase the risk of organ damage. Additionally, corticosteroids may suppress immune responses critical for infection control. Therefore, the safety and efficacy of these combinations should rely on careful monitoring and clinical judgment. The urgent need for novel, safer, and more effective therapeutics is further complicated by the rarity of PAM, resulting in minimal interest from pharmaceutical companies and a lack of clinical trials [13]. Environmental changes, such as global warming and water scarcity, may further influence the distribution and incidence of *N. fowleri* infections, highlighting the need for increased awareness and research into this deadly pathogen [14,15]. Herein, we review recent literature from the last decade using Google Scholar and PubMed, and discuss the impact of climate change and global warming on *N. fowleri*, emphasizing how rising temperatures and increased freshwater exposure are contributing to the broader geographical spread of this deadly

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Article highlights

- *N. fowleri* infections are rare but fatal, and with rising global temperatures, the geographic distribution of these amebae may advance, increasing the risk of infections in new regions. Climate change may directly influence water temperature, making *N. fowleri* more prevalent in previously unaffected areas, requiring enhanced monitoring and public health measures.
- Advances in treatment strategies for *N. fowleri* include the use of nanotechnology, which enhances the efficacy of established therapies such as amphotericin B. Drug repurposing efforts have identified FDA-approved compounds like corifungin, a fungal protein synthesis inhibitor, and auranofin, an anti-rheumatic drug, as potential treatments, offering new hope for more effective and accessible options.
- Intranasal delivery of anti-amebic drugs, especially amphotericin B, offers a targeted and less toxic approach to treating *N. fowleri* infections, aligning with the parasite's natural route of entry. This method significantly reduces systemic toxicity compared to intravenous administration, though optimizing dosage and formulation remains a challenge.
- Emerging diagnostic methods, including PCR-based assays and antigen detection, are improving early detection and enabling better environmental surveillance. Identifying *Meiothermus* species as ecological markers of *N. fowleri* presence in water systems is a key development, supporting proactive water safety interventions.
- Despite promising treatment developments, clinical trials for *N. fowleri* therapies remain limited due to the rarity and rapid progression of the disease. The lack of large-scale patient populations complicates traditional trial designs, requiring innovative approaches such as compassionate use protocols and well-characterized animal models to advance therapeutic evaluation.

pathogen. We then discuss current clinical treatments and emerging therapeutic strategies, highlighting recent advances in drug repurposing and nanotechnology-based delivery systems. Finally, we reflect on recent patents, innovative technologies, and future challenges, offering a multidisciplinary perspective to guide continued research and strengthen public health preparedness against PAM.

1.1. Emerging hotspots and global distribution of *N. fowleri*

Historically, *Naegleria fowleri* infections were predominantly reported in the southern United States, particularly in regions with warm climates and freshwater exposure [16,17]. However, recent years have seen a noticeable shift in the geographical distribution of cases and environmental detections, raising concerns about an expanding ecological niche for this thermophilic ameba [15].

As of 2023, the Centers for Disease Control and Prevention (CDC) reported 164 cases of PAM in the United States since 1962, with only four survivors [18]. Globally, a recent review identified 488 reported cases of PAM since 1962, with the highest numbers in the United States of America, Pakistan, and Australia [19]. These figures likely underestimate the true burden, as many cases go undiagnosed or unreported due to limited awareness and diagnostic challenges, particularly in resource-limited settings where encephalitis cases may be misdiagnosed or go undocumented due to overlapping clinical symptoms with bacterial meningitis and challenges associated with postmortem examinations [3].

Recent case reports and environmental findings have emerged from several countries beyond traditional endemic zones. In Asia, infections have been documented in Bangladesh, India, Pakistan, and Taiwan, often linked to religious ablution practices or the use of untreated water for bathing [19]. In Western Asia, including countries like Turkey, and in parts of Africa such as Zambia, cases have been reported. Notably, China has also documented sporadic infections, suggesting a wider Asian distribution than previously recognized [20–22].

In March 2024, health officials in Western Australia issued a warning after *N. fowleri* was detected in Drakesbrook Weir, a popular freshwater recreational site in Waroona [23]. This marked a significant detection in a non-endemic region, prompting renewed public health scrutiny and water safety advisories. Similar northward shifts in the U.S.A., including recent infections in states such as Minnesota and Indiana, support the hypothesis that rising global temperatures may be enabling the ameba to persist in previously inhospitable environments [24–26].

The apparent expansion of *N. fowleri* may be attributed to several converging factors. Climate change has led to warmer freshwater bodies and extended warm seasons, creating more favorable conditions for the ameba's survival and proliferation [15]. Improved surveillance systems and diagnostic capabilities have enhanced detection, especially in regions that may have previously underreported cases. Rapid population growth and urbanization may have placed stress on water infrastructure, increasing the likelihood of human exposure to contaminated water sources. Additionally, greater awareness among clinicians, researchers, and public health officials may have contributed to more accurate and timely identification of infections.

Thus, global monitoring, standardized diagnostic protocols, and public health interventions tailored to both endemic and non-endemic regions are of utmost importance. As *N. fowleri* continues to adapt to changing environments, coordinated efforts are essential to map its distribution and inform mitigation strategies.

1.2. Current treatment strategies

Currently, the approved and clinical standard treatment for PAM includes a combination of amphotericin B, miltefosine, azoles such as fluconazole and voriconazole, and rifampin [8]. Amphotericin B is a polyene antifungal that disrupts the ameba's membrane integrity but is associated with significant nephrotoxicity [27,28]. It works by binding to ergosterol, an essential component of the ameba's cell membrane, leading to membrane disruption and cell death. However, its nephrotoxicity remains a significant concern, limiting its use. To mitigate this, liposomal formulations of amphotericin B have been developed, which may reduce kidney-related side effects but come at a higher cost [12]. Despite these advances, the high toxicity of amphotericin B means it is typically used in combination with other drugs to improve outcomes and reduce side effects. Miltefosine, originally developed as an anti-leishmanial drug, has demonstrated amebicidal activity and has improved survival in some cases. Azoles, including fluconazole and voriconazole, function by inhibiting sterol

biosynthesis in the ameba, thereby disrupting membrane function [29–31]. Rifampin, a bactericidal antibiotic, has often been used in combination therapy, though its stand-alone effect against *N. fowleri* is limited [8].

There are four well-documented clinical cases of survival from PAM, all involving aggressive, early, and combination-based treatment regimens [32–35]. In each case, intravenous amphotericin B, both in its conventional deoxycholate form and its less nephrotoxic liposomal formulation, was a key component of therapy. Miltefosine, an investigational drug with amebicidal properties, was administered alongside other agents under emergency access protocols. Patients were also treated with azole antifungals such as fluconazole or voriconazole, and rifampin, which may offer additive or synergistic effects against *Naegleria fowleri*. In some of these clinical cases, azithromycin was included due to its potential anti-amebic activity. Corticosteroids, particularly dexamethasone, were used to control cerebral edema. Moreover, induced hypothermia was applied to manage intracranial pressure and inflammation, contributing to improved outcomes. These survivors emphasize the importance of rapid diagnosis, immediate initiation of multi-drug therapy, and intensive supportive care [32–35]. Though rare, survival is possible when treatment is started early and combines pharmacological and physiological strategies to target the pathogen and protect the central nervous system. However, given the significant advancements in medical diagnostics, drug development, and neurocritical care in recent decades, the extremely limited number of documented survivors highlights a critical unmet need. Current therapeutic strategies remain inadequate, highlighting the urgency for more effective and accessible interventions for PAM.

1.3. Emerging therapies: nanotechnology and drug repurposing

Nanotechnology may offer considerable potential in the development of effective therapeutics against *N. fowleri*. Recent studies have demonstrated that combining conventional anti-amebic agents, such as amphotericin B, fluconazole, or nystatin, with silver nanoparticles may significantly enhance their efficacy at low micromolar concentrations [36]. For instance, amphotericin B at 2.5 µM, when combined with silver nanoparticles, exhibited a marked amebicidal activity within 24 hours. Similarly, the combination of oleic acid and silver nanoparticles has been shown to significantly reduce amebic viability and increase cytopathogenic effects on host cells [37].

Silver and gold nanoparticles have also been employed to improve drug bioavailability and antimicrobial activity. Guanabenz acetate, when conjugated with either silver or gold nanoparticles, showed enhanced amebicidal efficacy at concentrations as low as 2.5 µM [38]. Green-synthesized nanoparticles, stabilized using plant-derived polysaccharides and conjugated with natural flavonoids such as hesperidin and naringin, demonstrated significant activity against *N. fowleri*, surpassing the effects of traditional treatments like amphotericin B [39]. These findings highlight the potential of nanoparticle-based systems to amplify the therapeutic action of both existing and novel compounds.

Recent advancements have furthered the potential of nanoparticle-conjugated compounds. A 2024 study demonstrated that silver nanoparticles conjugated with terpenes such as farnesol, borneol, and andrographolide exhibited potent amebicidal activity, with IC_{50} values around 26.35 µM [40]. These nanoconjugates not only reduced trophozoite viability but also effectively targeted cyst forms, all the while maintaining minimal cytotoxicity toward human keratinocyte cells, suggesting the potential of nanoparticle-terpene formulations as innovative therapeutic agents for PAM.

In parallel, drug repurposing has emerged as a promising strategy to address the limited pipeline of anti-amebic therapies. The ReFRAME drug repurposing library, developed by the California Institute for Biomedical Research, comprises approximately 12,000 small molecules including FDA-approved drugs, investigational candidates, and preclinical agents. Screening of this library led to the identification of 90 compounds with activity against *N. fowleri*, 19 of which demonstrated rapid inhibitory effects within 24 hours [41]. Given that the majority of these compounds have already undergone preclinical safety assessments or clinical development, this approach provides a valuable framework for the expedited discovery of effective treatments for primary amebic meningoencephalitis.

Additional studies utilizing the COVID Box, a collection of 160 compounds, identified several agents with significant *in vitro* amebicidal activity against *N. fowleri* [42]. Notably, terconazole, clemastine, ABT-239, and PD-144418 demonstrated higher selectivity against the parasite. These compounds induced programmed cell death in *N. fowleri*, characterized by chromatin condensation, altered membrane permeability, disrupted mitochondrial membrane potential, and increased reactive oxygen species production, highlighting their potential as effective treatment options [42].

Debnath and authors have made notable contributions to anti-*Naegleria* drug discovery through repurposing strategies that focus on FDA-approved compounds. In a 2012 study, they identified corifungin, a polyene macrolide antifungal, via high-throughput screening as a potent amebicidal agent. Importantly, corifungin demonstrated *in vivo* efficacy in a murine model of *N. fowleri* infection, significantly improving survival rates and reducing brain pathology compared to controls and even outperforming amphotericin B in some parameters [43]. In another study, auranofin, a gold-containing compound approved for rheumatoid arthritis, revealed potent *in vitro* activity against multiple genotypes of *N. fowleri* by targeting thioredoxin reductase and disrupting the parasite's redox balance [44]. It also exhibited synergistic effects with amphotericin B, suggesting its potential in combination therapy; however, its efficacy has not yet been validated *in vivo* against *N. fowleri*.

Although numerous *in vitro* studies have evaluated therapeutic agents against *N. fowleri*, *in vivo* research remains relatively limited, despite its essential role in advancing candidates toward clinical application. A notable *in vivo* study explored the immunoprotective potential of two vaccine antigens delivered intranasally in a murine model mimicking *Naegleria*-induced meningitis [45]. One candidate was a 19 kDa polypeptide, and the other a peptide from the MP2CL5 membrane protein, both administered with cholera toxin as an adjuvant. The vaccines elicited strong immune responses in mice, with protective

antibody activity detected in serum and nasal washes [45]. In another study, researchers examined the infectivity of *N. fowleri* cysts in a murine model and found that cysts failed to initiate infection *in vivo* [46]. The study also investigated the role of cyclic AMP (cAMP) in the encystment process. Exposure of trophozoites to dipyridamole, a phosphodiesterase inhibitor, significantly increased intracellular cAMP levels and accelerated encystment. These results suggest that cAMP may play a key role in regulating encystment, offering insights into the biology of *N. fowleri* and potential new intervention strategies [46].

Another notable recent study focused on nitroxoline, an antibiotic historically used in Europe for urinary tract infections [47]. The *in vitro* study demonstrated that nitroxoline exhibits amebicidal activity against *N. fowleri*, inducing programmed cell death at low micromolar concentrations without significant cytotoxicity to human cells [47]. Recently, phosphonate inhibitors of human enolase 2 (ENO2), originally developed for glioblastoma multiforme (GBM), have emerged as promising compounds. These inhibitors have demonstrated efficacy in rodent models of GBM and are well tolerated in mammals, as enolase 1 (ENO1) is the predominant isoform used systemically [48]. The study explored the potential of these ENO2 inhibitors in treating *N. fowleri* infections. Notably, (1-hydroxy-2-oxopiperidin-3-yl) phosphonic acid (HEX) was identified as a potent inhibitor of *N. fowleri* ENO (NfENO), exhibiting an IC50 value of 0.14 ± 0.04 μM and an EC50 value of 0.21 ± 0.02 μM for trophozoite toxicity. Importantly, HEX displayed a favorable cytotoxicity profile. Molecular docking simulations further revealed that HEX binds strongly to the active site of NfENO. *In vivo*, intranasal delivery of HEX improved the survival of *N. fowleri*-infected rodents. Animals treated with 3 mg/kg HEX for 10 days showed significantly extended survival, with eight of 12 treated animals remaining alive after one week of observation, compared to only one of 12 vehicle-treated rodents. Despite this, HEX was not curative, as six of the eight surviving rodents still harbored amebae in their brains. These findings highlight the potential of HEX as a lead compound for PAM treatment [48]. These studies emphasize the importance of drug repurposing and also highlight the need for further preclinical development and *in vivo* validation. These findings collectively provide a promising outlook on the future of treatments for *N. fowleri* infections, with a multifaceted approach encompassing nanotechnology, drug repurposing, and novel synthetic compounds showing significant potential in the fight against this deadly pathogen.

1.4. Intranasal administration as a therapeutic avenue

Given that *N. fowleri* typically enters through the nasal passages and migrates along the olfactory neuroepithelium to the brain, intranasal delivery offers a rational and targeted approach for therapeutic intervention [13,49]. As already discussed, while amphotericin B demonstrated potent anti-amebic activity *in vitro* by disrupting ergosterol synthesis, its clinical efficacy is hampered by poor blood–brain barrier permeability and systemic toxicity when administered intravenously [12,27,28]. High intravenous (IV) doses are often required to reach effective CNS concentrations, but this frequently leads to hepatotoxicity and nephrotoxicity due to off-target accumulation [8]. As clinical trials are not feasible for PAM, *in vivo* studies and data from clinical case studies can be utilized. Recent *in vivo* studies have compared intravenous versus intranasal delivery of amphotericin B, showing that intranasal administration significantly reduces adverse effects on vital organs such as the liver, kidney, and brain in a murine model [49]. This method aligns with the parasite's natural entry through the nasal cavity, supporting its rationale for therapeutic use. The findings suggest the potential for repositioning amphotericin B for intranasal administration in managing PAM. Nonetheless, optimizing dosage, frequency, and formulation for this delivery route will be needed to improve patient outcomes and reduce treatment-associated side effects, supporting further exploration of nasal routes to enhance drug bioavailability in the CNS while limiting systemic toxicity [49].

Additionally, the use of nasal inhalers to deliver vaporized anti-*N. fowleri* drugs has been suggested [50]. This method may allow for self-administration, faster onset of action, and potentially prophylactic use in high-risk settings. This method could offer multiple advantages, including rapid onset of action through direct access to the CNS via the olfactory epithelium. Moreover, co-administration with anti-inflammatory agents such as dexamethasone may aid in managing elevated intracranial pressure, a critical and often fatal complication of PAM. However, translating this concept into clinical use requires a series of systematic preclinical and clinical steps. Detailed pharmacokinetic and pharmacodynamic profiling is needed to assess whether vaporized agents can reach therapeutic concentrations in brain tissues without causing local or systemic toxicity. The physicochemical properties of candidate compounds must also be suitable for aerosolization, with sufficient stability and solubility to maintain activity during nebulization and delivery.

Future *in vivo* efficacy studies using established animal models of PAM will be critical to optimize dosing, delivery frequency, and formulation parameters such as particle size, carriers, or solubilizers. Safety assessments should include repeated-dose studies to evaluate local and systemic effects, especially given the sensitive nature of nasal mucosa and proximity to the central nervous system. Due to the rarity and rapid progression of PAM, conventional clinical trials are not feasible due to the rarity and high fatality of the disease. Instead, other approaches such as efficacy study of novel compounds by well-characterized animal models, human safety study by Phase 1 clinical trial, and compassionate use protocols may advance therapeutic evaluation. Collaborations between academia, industry, and public health authorities will be important for ensuring device–drug compatibility, Good Manufacturing Practice (GMP)-grade production, and emergency use preparedness. In summary, while intranasal delivery of anti-amebic drugs presents an innovative route for intervention, further development and robust validation, real-world case documentation, and coordinated efforts to ensure readiness for rapid deployment in emergency scenarios are needed.

1.5. Emerging tools and indicators for managing *N. fowleri* risk in water supplies

Despite growing awareness of *N. fowleri* as a serious public health threat, its surveillance remains absent from global water quality monitoring frameworks. Current assessments typically focus on bacterial indicators like *E. coli* and select enteric pathogens such as norovirus, *Giardia*, and *Cryptosporidium* [51,52]. However, given the free-living nature of *N. fowleri*, association with water exposure, and high fatality rate, its inclusion in water surveillance programs warrants urgent attention, especially in regions reliant on domestic storage tanks and ablution practices [3].

Recent studies have validated *Meiothermus* species as promising ecological markers for *N. fowleri* colonization in drinking water distribution systems [53]. In one of the most comprehensive longitudinal studies to date, over 230 samples collected across a 300 km network over three years confirmed that operational taxonomic units assigned to *Meiothermus chliarophilus* and *M. hypogaeus* were significantly associated with *N. fowleri* presence. Laboratory experiments further demonstrated that *Meiothermus* species support *N. fowleri* growth in biofilms, suggesting a functional ecological relationship beyond mere correlation. These findings elevate *Meiothermus* from a putative to a validated biomarker, offering water utilities a tool for targeted risk assessment and early intervention [53]. In addition, while direct evidence is limited, warm, eutrophic waters that support cyanobacterial blooms may also create favorable conditions for *N. fowleri*, making cyanobacteria a potential ecological indicator of increased ameba risk [14].

Recently it was suggested that iron availability may be as crucial as temperature in shaping the pathogenicity and ecological success of *N. fowleri* [54]. It was suggested that iron-rich conditions may tip the balance toward pathogenic forms, particularly in environments where warm temperatures already favor trophozoite proliferation, raising concerns about regions experiencing shifts in rainfall, erosion, or groundwater dynamics that release stored iron into water bodies. The study also explores how iron might enable *N. fowleri to* tolerate or adapt to low-oxygen conditions, pointing to iron-sulfur enzymes, anaerobic pathways, and a potential denitrification system encoded in its genome. These adaptations could extend its survivability into microoxic, or anoxic niches previously thought inhospitable. It is proposed that climate change, through warming waters, increased runoff, and freshwater acidification, may enhance iron solubility and further bolster *Naegleria's* resilience, while elevated iron levels may also reduce disinfectant efficacy in water systems, weakening public health protections and highlighting the need for integrated environmental monitoring [54].

In parallel, low-cost technological interventions are being explored. Novel micelle clay complexes containing montmorillonite clay and activated carbon have shown potential for eliminating amebae which could be used in water sources, for integration into taps and portable containers [55]. Deep eutectic solvents, a class of biodegradable and economical antimicrobials, have also demonstrated broad-spectrum efficacy against pathogens, including amebae. While their potential application in treating water contaminated with *N. fowleri* is promising, further safety and toxicity assessments are needed. Together, biomarker-based detection and innovative disinfection technologies offer a forward-looking strategy to monitor and mitigate *N. fowleri* in vulnerable water systems [56].

1.6. Recent advances in diagnostic techniques for *N. fowleri* and emerging patents

Diagnosing *N. fowleri* infections presents significant challenges due to the pathogen's rare occurrence and the rapid progression of PAM [57]. Traditionally, diagnosis has relied on methods such as cerebrospinal fluid (CSF) analysis, microscopy, and culture, with PCR-based assays gaining traction for their high sensitivity and specificity. However, recent advancements over the past two years have shown promising improvements in diagnostic techniques, enhancing early detection, environmental surveillance, and the potential for rapid, point-of-care testing.

One notable development is the ongoing research into antigen-based diagnostic methods. In a recent in silico study, several *N. fowleri* proteins (Mp2CL5, Nfa1, Nf314, proNP A and proNP B) were identified potential vaccine candidates [58]. Through computational analyses, three highly antigenic epitopes (EAKDSK, LLPHIRILVY and FYAKLLPHIRILVYS) were selected, leading to the design of a multi-epitope peptide vaccine, termed NaeVac. The identification of antigenic proteins, such as those targeted in this multi-epitope peptide vaccine, could facilitate the development of new diagnostic assays that are more rapid and specific [58]. These assays would allow for more efficient detection of *N. fowleri* in both clinical and environmental samples. Additionally, IEH Laboratories & Consulting Group introduced an RT-PCR test in 2022 that can detect *N. fowleri* in environmental samples within two days [59]. Following CDC protocols for sample preparation and DNA extraction, this test is a method for monitoring recreational water sources for the pathogen. These advancements indicate a promising future for diagnostic methods that are crucial for controlling *N. fowleri* infections and improving patient outcomes.

Recently, we reviewed a number of patents over the last five years that could be utilized for use against *N. fowleri* [60–63]. Notable advancements include the use of methods to enhance the efficacy of antimicrobial agents using ultrasound (Acoustic Cluster Therapy). Another promising patent explores the use of chimeric antigen receptors (CARs) to target and clear pathogens, including *Naegleria*, via phagocytosis [60]. For water treatment, a number of inventions aim to address the presence of *N. fowleri* in public water systems. These include methods for regenerating ion exchange materials used in water treatment, though one such invention has been abandoned. Other inventions focus on improving disinfection methods for large water bodies, such as swimming pools, where *N. fowleri* is commonly found. On the diagnostic front, recent patents have developed methods for detecting biomarkers using light scattering microscopy, and innovations in metagenomic next-generation sequencing (mNGS) offer a broad and rapid approach for diagnosing infections, including PAM caused by *Naegleria* [60–63]. However, many of these patented technologies remain in preclinical stages, underscoring the need for translational research, regulatory

streamlining, and multisector collaboration to bring these innovations from bench to field.

2. Conclusion

In conclusion, while current treatments for *N. fowleri* are limited, there is significant promise in emerging therapies and drug delivery systems [64–69]. A recent study emphasized the roles of rising temperatures, antimicrobial resistance, the ameba's ability to harbor other microorganisms, and the limitations of conventional disinfection methods, such as chlorination, in exacerbating the impact of *N. fowleri*, calling for a holistic One Health perspective [67]. Intranasal administration, nanotechnology, and adjunctive therapies represent exciting directions for improving outcomes in PAM, but there remain numerous challenges related to drug formulation, delivery, and cost that must be overcome. In addition, the rise of *N. fowleri* cases due to climate change emphasizes the need for early detection, improved diagnostics, and better environmental controls to reduce exposure. Importantly, the difficulty of early and accurate diagnosis remains a critical barrier to effective management of PAM. Future efforts should prioritize the development of rapid, sensitive, and accessible diagnostic tools alongside innovations in treatment and prevention to improve patient outcomes and reduce the global burden of this devastating disease. The future of *N. fowleri* treatment and prevention lies in a multifaceted approach that combines innovative drug development with enhanced surveillance, collaborative research, and a global commitment to addressing the health impacts of climate change.

3. Expert opinion

Despite significant research, effective treatments for PAM due to *N. fowleri* remain limited, and the high mortality rate associated with the disease highlights the need for more accessible, efficacious, and less toxic therapeutic options [70–74]. The treatment landscape has been dominated by the use of amphotericin B, which remains the gold standard, but its clinical use is hampered by severe side effects, particularly nephrotoxicity and hepatotoxicity, especially when administered intravenously [75–77]. This is compounded by the challenge of ensuring adequate CNS concentrations due to the drug's poor blood–brain barrier penetration.

In recent years, promising alternative strategies have emerged, offering potential solutions to these challenges. One such avenue is intranasal drug delivery, which leverages the natural route of infection through the nasal passages. This approach has shown promise in improving the drug's delivery to the CNS while reducing systemic toxicity. Studies in murine models have demonstrated that intranasal administration of amphotericin B can bypass the blood–brain barrier more effectively than intravenous administration, thus potentially reducing the dose required and minimizing the side effects associated with high systemic concentrations. However, while these studies are promising, further studies are necessary to optimize the formulation and dosing for human application.

Another area of exploration is the development of adjunctive therapies, such as the co-administration of anti-inflammatory agents like dexamethasone, which could help manage elevated intracranial pressure, a common complication of PAM. Additionally, drug repurposing, where existing medications are evaluated for their activity against *N. fowleri*, could offer a faster route to clinical application. Nanotechnology has also garnered attention, with nanoparticle-based drugs showing promise in overcoming the blood–brain barrier and improving drug delivery to the brain [78–81]. These innovative approaches, however, require extensive validation in animal models and human trials before they can be widely implemented.

Despite these advances, several barriers to implementation remain. The rarity of PAM means that large-scale clinical trials are difficult to conduct, and much of the available data come from case reports or small-scale studies. This limits the evidence for the widespread use of new treatments and complicates regulatory approval processes. Moreover, logistical challenges, including the high cost of developing and manufacturing advanced therapies like nanoparticles or intranasal formulations, could make these treatments less accessible, particularly in low-resource settings where *N. fowleri* is most prevalent.

Furthermore, climate change will likely have a dual role in both complicating treatment and advancing research [82,83]. As rising temperatures may increase the number of *N. fowleri* cases, there is a growing need for innovative therapeutic strategies. However, the changing environment may also necessitate new approaches to disease management, including the incorporation of environmental monitoring and more rapid diagnostic tools [84–86]. Advances in diagnostic techniques, such as RT-PCR and antigen-based assays, could enable earlier detection, which is critical for improving patient outcomes. The development of more sensitive and rapid diagnostic tests will not only help clinicians initiate appropriate treatment sooner but also aid in identifying and mitigating risk factors in water supplies. Moreover, with the growing focus on climate change, the development of more effective water treatment and surveillance systems to prevent *N. fowleri* exposure should become a priority.

Of note, the majority of PAM cases are linked to waterborne exposure, but evidence suggests that *N. fowleri* may also be transmitted through inhalation of cyst-laden dust, known as the 'dry infection' route, which may account for around 6–8% of reported cases [15]. Cysts in fine dust or clay may enter the nasal passages, excyst, and invade the brain. Although desiccated cysts are thought to be short-lived, studies show they can survive longer when embedded in fine clay, increasing their potential for airborne transmission in arid environments. These findings highlight the need to consider both wet and dry transmission routes, especially as dust storms may become more common with climate change [15].

As we look to the future, the treatment of *N. fowleri* infections will increasingly rely on interdisciplinary research [87]. The integration of climate science with infectious disease research will be critical in understanding how environmental changes affect the pathogen's spread and how to mitigate its

impact [88,89]. Moreover, collaborations between researchers, clinicians, public health authorities, and the water industry will be necessary to develop novel therapeutic strategies, enhance surveillance, and ensure that treatments are accessible and effective [90–93].

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

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