Primary Amebic Meningoencephalitis (PAM) — Comprehensive Disease Profile

MONDO: MONDO:0000290 · **Category:** Infectious disease · **Causal agent:** *Naegleria fowleri* (free-living thermophilic amoeba; NCBI Taxon:5763)

> **Causal "gene" note.** PAM is **not a human genetic disease** and has **no human causal gene**. The template's "Causal gene(s): not recorded" field is correct and expected: the disease is produced by infection with the free-living amoeba ***Naegleria fowleri***. Where this report refers to "causal genes," these are **pathogen (amoeba) virulence genes** (e.g., *nfa1*, naegleriapore/*Npa*, cathepsin/serine-protease genes), not host germline genes. All subsequent sections should be read with the pathogen as the etiologic agent.

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1. Disease Information

Overview. Primary amebic meningoencephalitis (PAM) is a rapidly progressive, fulminant, almost universally fatal infection of the central nervous system caused by the thermophilic, free-living amoeba *Naegleria fowleri* ("brain-eating amoeba"). Infection occurs when warm fresh water containing the amoeba is forced into the nose; the organism crosses the cribriform plate along the **olfactory nerve** and invades the brain, producing a hemorrhagic, necrotizing meningoencephalitis (P 22919000). Death typically occurs within ~1–2 weeks of symptom onset, with a case-fatality rate >95–97% (P 39432113).

Key identifiers. - **Mondo:** MONDO:0000290 - **ICD-10:** B60.2 (Naegleriasis / primary amebic meningoencephalitis) - **ICD-11:** 1F55 (Acanthamoebiasis / free-living amoeba infections) → *Naegleria* meningoencephalitis - **MeSH:** D008836 *Meningoencephalitis*; organism MeSH D009258 *Naegleria*; D054314 *Central Nervous System Protozoal Infections* - **SNOMED CT:**

36649002 (Primary amebic meningoencephalitis) - **Orphanet:** Not a classic rare-genetic ORPHA entry; covered under free-living amoebic infections - **OMIM:** Not applicable (no Mendelian locus) - **NCBI Taxonomy (agent):** *Naegleria fowleri* Taxon:5763

Synonyms / alternative names. Naegleriasis; *Naegleria fowleri* infection; "brain-eating amoeba" infection; amebic meningoencephalitis (primary); PAM; PAME.

Information source type. Disease-level, aggregated from **case reports, CDC Free-Living Ameba (FLA) surveillance, and systematic reviews** (P 32369575). P 26582886
Because PAM is extremely rare, there are no large EHR cohorts; evidence is predominantly individual case/autopsy data pooled at the disease level.

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2. Etiology

Primary cause (infectious). The sole cause is infection with *Naegleria fowleri*, a thermophilic free-living amoeba found worldwide in warm fresh water (lakes, ponds, rivers, hot springs, geothermal water) and in inadequately disinfected recreational/treated water (pools, splash pads, tap water) (P 40146665 P 22919000). P 27123690
The amoeba has three life stages: **trophozoite** (invasive, feeding), **flagellate** (transient), and **cyst** (environmentally resistant). Only the trophozoite invades tissue.

Route of entry. Intranasal instillation of contaminated water (swimming, diving, splashing, hot-spring bathing, **religious ablution/wudu**, and **nasal/sinus irrigation with neti pots using contaminated tap water**) (P 22919000). P 21291600

In Karachi, Pakistan, a cluster of 13 PAM cases occurred in people with **no aquatic exposure**, with infection attributed to **ablution with tap water**; N. fowleri was subsequently detected in Karachi municipal tap water (11/39 samples) under conditions of high temperature, low chlorine, and high coliform counts (P 21291600). P 39780139

Risk factors (environmental/behavioral). - **Warm-freshwater nasal exposure** — strongest risk; swimming/diving is the most common exposure and lakes/ponds/reservoirs the most common source (P 32369575).
- **Male sex** (~75–76% of cases) (P 32369575). P 26582886
- **Young age** (children/adolescents; median 12–14 years) (P 32369575). P 26582886
- **Warm climate / summer months / southern latitudes**, with geographic expansion northward attributed to climate warming (P 22919000). P 26582886
- **Inadequately disinfected treated water** (splash pads, pools, household plumbing) (P 40146665). P 22919000
- **Nasal irrigation with non-sterile tap water** (P 22919000).

Genetic risk/protective factors (host). None established — PAM is not a heritable disorder and no human susceptibility/protective loci are validated. (Not applicable.)

Protective factors (environmental). Keeping water out of the nose; using nose clips; using sterile/distilled/boiled water for nasal irrigation; adequate water chlorination (free chlorine ≥1 ppm) — all reduce risk (CDC guidance; P 40146665).

Gene–environment interactions (host). Not applicable (no human genetic component). The relevant interaction is **pathogen virulence gene expression × host nasal exposure/temperature**: thermophilic growth (optimal ~42–45 °C) and virulence-gene upregulation on contact with host cells drive invasion (P 40096149; P 33843581).

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3. Phenotypes

PAM is clinically **biphasic**, progressing from nonspecific flu-like illness to fulminant meningoencephalitis (P 26582886).

Onset is **acute**, typically 1–9 days (median ~5 days) after exposure; course is **rapidly progressive**, death in a median of ~5 days from symptom onset.

Phenotype	Type	Frequency	HPO suggestion
Fever	symptom/ sign	~79–92%	HP:0001945 Fever
Headache (severe, frontal)	symptom	~58–83%	HP:0002315 Headache
Nausea / vomiting	symptom	common/high	HP:0002018 Nausea; HP:0002013 Vomiting
Nuchal rigidity / meningismus	sign	common	HP:0031179 Nuchal rigidity
Altered mental status / confusion	sign	~50%+	HP:0001298 Encephalopathy
Seizures	sign	~41%	HP:0001250 Seizure
Photophobia	symptom	common	HP:0000613 Photophobia
Anosmia / altered taste/smell	sign	early, characteristic	HP:0000458 Anosmia
Coma	sign	late	HP:0001259 Coma
Cranial nerve palsies, raised ICP	sign	late	HP:0002493 Upper motor neuron dysfunction; HP:0002118 (↑ICP-related)

Frequencies from Indian systematic review (fever 79.2%, headache 58.3%, seizures 41.6%; P 42764041) and Kerala series (fever 91.7%, headache 83.3%, altered mental status 50%; P 41873284).

Laboratory-abnormality phenotypes (CSF). Resembles bacterial meningitis: elevated opening pressure, **neutrophilic pleocytosis** (median 2400 cells/μL), **low glucose** (median 23 mg/dL), **high protein** (median 365 mg/dL); **motile trophozoites on wet mount** are diagnostic (P 26582886).

HPO: HP:0002922 Increased CSF protein; HP:0003112 (abnormal CSF); low CSF glucose.

Severity / progression. Uniformly **severe** and **progressive**; essentially no stable or episodic course. **Quality-of-life impact:** for the few survivors, outcomes range from full recovery to severe neurological sequelae (cognitive, motor deficits); for the vast majority the outcome is death, so QoL instruments (EQ-5D/SF-36) are not meaningfully applied at the population level.

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4. Genetic / Molecular Information

Human causal genes: None (not a genetic disease).

Pathogen (amoeba) "virulence genes" (the functional equivalent of causal molecular drivers): - ***nfa1*** — encodes a ~13.1 kDa pseudopod/food-cup protein central to contact-dependent cytolysis; a validated virulence/vaccine antigen (P 22955499).
- **Naegleriapores / *Npa* (A and B)** — pore-forming, membrane-permeabilizing polypeptides causing host-cell lysis (P 39432113).
- **Cathepsin B and serine/cysteine proteases** — degrade host extracellular matrix and tissue; secreted and packaged in extracellular vesicles (P 39432113) (P 40312759).
- **Leishmanolysin (GP63-like metalloprotease)** — adhesion/enzymatic virulence, identified in EV proteome (P 40312759).
- **Mp2CL5** membrane protein; **lysozyme, cystatin, hemerythrin** (host-defense evasion, brain migration, lethal infection) (P 40096149).
- **Lectins** mediating adhesion (P 32716210).

Genome. *N. fowleri* genome sequenced; comparative genomics distinguishes pathogenic *N. fowleri* from non-pathogenic *N. gruberi*, though several "virulence" homologs are shared, implying regulation/expression (not mere presence) determines pathogenicity (P 33843581). P 31797948).

Variant classification / allele frequency / somatic-vs-germline / modifier genes / epigenetics / chromosomal abnormalities (human): Not applicable — there are no human pathogenic variants, ClinVar entries, gnomAD frequencies, or chromosomal findings for this infectious disease.

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5. Environmental Information

- **Environmental reservoir:** warm fresh water worldwide — lakes, ponds, rivers, hot springs, geothermal discharge, poorly maintained pools/splash pads, and warm tap/plumbing water (P 40146665). P 22919000). Thermophilic: thrives up to ~45 °C.
- **Climate sensitivity:** warming water temperatures expand the amoeba's range; northward spread of US cases documented (P 22919000). P 26582886).
- **Lifestyle/behavioral factors:** recreational freshwater activities (swimming, diving, water-skiing, splash pads), hot-spring bathing, and **nasal/sinus irrigation** with untreated tap water (P 22919000).
- **Infectious agent (NCBI Taxonomy):** *Naegleria fowleri* (Taxon:5763), phylum Percolozoa, class Heterolobosea. Related non-pathogenic congener: *N. gruberi*. Other pathogenic FLA

causing distinct CNS disease: *Acanthamoeba* spp., *Balamuthia mandrillaris* (granulomatous amebic encephalitis), *Sappinia*
( ).
P 33843581

6. Mechanism / Pathophysiology

Ordered causal chain (initiating exposure → clinical manifestation):

1. **Contaminated warm freshwater is forced into the nasal cavity** (swimming, diving, hot-spring bathing, or nasal irrigation) → deposits *N. fowleri* trophozoites on the **olfactory/nasal mucosa** (*demonstrated*,
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P 22919000
2. Trophozoites **adhere to nasal mucosa** via lectins/food-cup (Nfa1) structures and begin feeding on epithelium → local mucosal damage (*demonstrated in vitro/animal*,
P 32716210
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P 22955499
3. Amoebae **migrate along olfactory nerve fibers through the cribriform plate** into the olfactory bulbs (*demonstrated; explains early anosmia*,
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P 22919000
4. In the CNS, trophozoites perform **contact-dependent trogocytosis/phagocytosis ("food-cup" ingestion of neural cells)**, driven by **actin dynamics regulated by Arp2/3 and Src kinase** (*demonstrated*,
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P 40096149
5. Simultaneously, **contact-independent cytolysis** occurs via secreted and **extracellular-vesicle–delivered virulence factors** — naegleriapores (pore formation), cathepsin B/serine proteases, phospholipases, leishmanolysin — causing **hemolysis, increased membrane permeability, and necrosis** (*demonstrated in vitro*,

P 40312759

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P 39432113

6. Tissue destruction + amoebic antigens **trigger a massive innate inflammatory response** (neutrophil and eosinophil influx, cytokine release) → **necrotizing, hemorrhagic meningoencephalitis** with cerebral edema (*demonstrated; neutrophils central to host defense*,

P 2628288

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P 27525348

7. Cerebral edema and inflammation → **raised intracranial pressure**, uncal/tonsillar herniation → **brainstem compression** (*inferred from clinical/autopsy data*,

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P 25667249

8. → **Coma and death**, typically within days (*demonstrated clinical outcome*,

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P 26582886

Branch: Beyond primary olfactory-bulb invasion, autopsy and animal data indicate **extra-CNS hematogenous dissemination** can occur (relevant to transplant-transmission risk) (

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P 24279908

Molecular pathways / cellular processes. - Host-cell ingestion: **actin cytoskeleton remodeling (Arp2/3, Src kinase)** — GO:0030041 actin filament polymerization; GO:0006909 phagocytosis; "trogocytosis" (

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P 40096149

- Cytolysis: **pore-forming/membrane permeabilization** (naegleriapores) — GO:0051715 cytolysis in another organism; GO:0006887 EV/exocytosis. - Proteolysis: **cysteine/serine protease activity** — GO:0006508 proteolysis (

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P 39432113

- Metabolic shift: brain-passaged amoebae show altered **lipid storage/utilization** vs axenic culture (Raman microspectroscopy) (

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P 40096149

- Immune involvement: innate-dominant **neutrophilic/eosinophilic** inflammation; adaptive immunity can be protective in animal models (P 2628288). P 646016

Tissue-damage mechanisms: necrosis, hemorrhage, phagocytic "nibbling" of neurons, protease-mediated matrix degradation, oxidative inflammatory injury.

Molecular profiling (transcriptomics/proteomics). RNA-seq across life stages shows stage-specific regulation of the cytoskeletal machinery: **nf-profilin** (actin-binding regulator) is high in cysts and membrane-localized, whereas **nf-actin** localizes to cytoplasm, pseudopodia, and **food-cup** structures of trophozoites; during cyst→trophozoite conversion on host-cell contact, profilin falls and actin rises — directly linking the transcriptome to the invasive food-cup apparatus (P 40016342). P 36839446

Secretome/EV proteomics identified >1000 proteins including leishmanolysin and serine proteases (P 40312759).

Brain-passaged vs axenic amoebae differ metabolically in lipid storage/utilization (Raman spectroscopy) (P 40096149).

Transcriptomic profiling of the "brain-eating amoeba" host interaction further catalogs virulence-associated expression (P 39735262).

Phylogenomics places *N. fowleri* in phylum Heterolobosea, new order **Naegleriida** (P 39826589).

Suggested ontology terms: GO:0006909 (phagocytosis), GO:0030041 (actin polymerization), GO:0006508 (proteolysis), GO:0019835 (cytolysis), GO:0006954 (inflammatory response); CL:0000540 neuron, CL:0000127 astrocyte, CL:0000775 neutrophil; UBERON:0002264 olfactory bulb, UBERON:0000955 brain.

7. Anatomical Structures Affected

- **Primary organ: Brain** (UBERON:0000955), especially **olfactory bulbs** (UBERON:0002264), frontal lobes, and basal cisterns; **meninges** (UBERON:0002360). Nervous system (central).
- **Portal of entry tissue: nasal/olfactory epithelium** (UBERON:0001707 nasal cavity; UBERON:0001997 olfactory epithelium) and **cribriform plate / olfactory nerve** (UBERON:0001675).
- **Secondary / disseminated involvement:** rare extra-CNS spread (lung, heart, kidney reported at autopsy), relevant to transplant risk (P 24279908).
- **Tissue/cell level:** nervous tissue — **neurons** (CL:0000540), **astrocytes/glia** (CL:0000125); inflammatory infiltrate of **neutrophils** (CL:0000775) and **eosinophils** (CL:0000771).
- **Subcellular (host damage):** plasma-membrane disruption (pore-forming peptides); for the amoeba, **food cup / pseudopod (amoebic phagocytic structure)**, lysosomes/EVs (GO:0005764 lysosome; GO:1903561 extracellular vesicle).
- **Lateralization:** typically **bilateral** but may begin **asymmetric** reflecting unilateral olfactory-tract seeding; progresses to diffuse cerebral involvement.

8. Temporal Development

- **Onset: Acute**. Incubation ~1–9 days (median ~5) after nasal exposure (P 26582886).
- **Stages:** (i) **Early** — nonspecific flu-like: fever, headache, nausea/vomiting, altered smell/taste; (ii) **Late** — CNS: meningismus, confusion, seizures, focal deficits, coma (P 26582886).
- **Progression rate: Rapid/fulminant.** Median time from symptom onset to death ~5 days; most die within 1–2 weeks

(P 32369575). P 26582886

- **Course pattern:** monophasic, progressive; no relapsing–remitting or episodic form.
- **Duration/remission:** self-limited only in the sense of rapid death; **treatment-induced survival is rare** and depends on very early recognition (P 25667249).
- **Critical window for intervention:** the first **24–72 hours** after symptom onset — survival correlates with early diagnosis and immediate combination therapy (P 27525348). P 25667249

9. Inheritance and Population

- **Inheritance: Not applicable** (infectious; no germline transmission, penetrance, anticipation, founder effects, or carrier frequency).
- **Incidence/prevalence:** Extremely rare. **~0–8 US cases/year** (CDC); ~381 global cases reported through 2018 (P 32369575); ~142 US cases 1937–2013 (P 26582886). True incidence likely underestimated due to misdiagnosis.
- **Case-fatality rate:** **>95–97%**; only ~7 confirmed survivors globally in the 2018 review (P 32369575). P 39432113

- **Sex ratio:** male-predominant ~3:1 (75–76% male) (P 32369575). P 26582886
- **Age distribution:** predominantly **children and adolescents**, median 12–14 years, though cases span 13 days to 85 years (P 42764041).
- **Geographic distribution:** worldwide in warm climates; US cases concentrated in **southern-tier states** (Texas, Florida — Florida accounts for >25% of US cases) with **northward expansion** (Minnesota, Kansas, Indiana) linked to warming (P 23621053). P 22919000
  Substantial case loads reported from **Pakistan, India, Australia**, and other warm regions (P 42764041). P 41873284
  Pakistan (Karachi) is notable for a **non-recreational, ablution/tap-water–associated** disease pattern (13-case cluster; N. fowleri confirmed in municipal tap water), reflecting high ambient temperature, under-chlorination, and degraded distribution systems (P 21291600). P 39780139

10. Diagnostics

- **CSF analysis:** bacterial-meningitis-like profile — **neutrophilic pleocytosis, low glucose, high protein, raised opening pressure** (P 26582886).

- **Direct microscopy (first-line, rapid): wet-mount of fresh CSF** showing **motile trophozoites** — positive in 95.8% of Indian cases; Giemsa/Wright/trichrome staining (do NOT rely on Gram stain)
(P 42764041). P 23710088
- **Molecular confirmation: real-time PCR** of CSF/tissue (CDC) — definitive; **LAMP** assays for rapid water/clinical detection
(P 35020127). P 25822175
PCR confirmation is underused in resource-limited settings (only 2/24 Indian cases)
(P 42764041).
- **Culture:** CSF on non-nutrient agar with *E. coli* overlay; flagellation test (trophozoite→flagellate in distilled water)
(P 35020127).
- **Immunologic:** immunohistochemistry/indirect immunofluorescence on tissue; antigen detection.
- **Imaging:** CT/MRI shows nonspecific cerebral edema, basal meningeal enhancement, hemorrhage; often normal early
(P 26582886).
- **Clinical criteria / differential diagnosis:** PAM should be suspected in **acute meningoencephalitis with recent freshwater nasal exposure**
(P 40146665).
Differential: bacterial meningitis, viral/herpes encephalitis, fungal meningitis, tuberculous meningitis — distinguished by motile amoebae on wet mount and PCR, and by negative bacterial/viral cultures
(P 27123690).

- **Screening:** No asymptomatic screening exists (too rare, too rapid); environmental water testing (PCR/LAMP) supports outbreak investigation (P 25822175).
- **Suggested LOINC concepts:** CSF cell count/differential, CSF glucose, CSF protein, *Naegleria* PCR.

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11. Outcome / Prognosis

- **Mortality:** **>95–97%**; historically near-uniformly fatal (P 32369575, P 39432113).
- **Survival:** only a handful of confirmed survivors worldwide; **3 well-documented North American survivors** by mid-2010s (P 25667249, P 27525348).
- **Prognostic factors: time to diagnosis and treatment** is the dominant determinant; early presentation (flu-like stage), prompt combination antimicrobials, aggressive ICP control, and therapeutic hypothermia are associated with survival (P 25667249, P 27525348).
- **Morbidity in survivors:** variable — from near-complete recovery to permanent neurological deficits (cognitive, motor, visual).
- **Complications:** cerebral edema, herniation, raised ICP, seizures, status epilepticus, hydrocephalus (P 25667249).
- **Disease-specific mortality:** essentially all deaths attributable directly to CNS infection within days–weeks.

12. Treatment

No single proven cure; management is a multidrug + neurocritical-care bundle started emergently on suspicion.

- **Amphotericin B** (polyene antifungal; amebicidal) — **backbone**, given **IV and intrathecal/intraventricular**; mainstay in nearly all regimens (used in 91.6% of Indian cases) (P 42764041). P 23710088
  NCIT: Amphotericin B (C280).
- **Miltefosine** (alkylphosphocholine; investigational, CDC-provided) — added to regimens of recent survivors (P 26679626). P 25667249
  NCIT: Miltefosine (C61769).
- **Adjunct antimicrobials:** azithromycin, fluconazole (or other azoles), rifampin — commonly combined (P 27525348).
- **Neurocritical care:** aggressive management of **elevated intracranial pressure** using traumatic-brain-injury principles, CSF diversion (intraventricular shunt), and **therapeutic (targeted) hypothermia** — credited in survivors (P 25667249). P 27525348
  NCIT: Therapeutic Hypothermia.
- **Supportive care:** mechanical ventilation, seizure control, dexamethasone for edema.
- **Treatment outcomes:** despite therapy, most cases are fatal; survival clusters around early-treated, miltefosine-containing, hypothermia-managed cases (P 26679626).

- **Experimental / preclinical pipeline:** A high-throughput phenotypic screen of 12,000 **ReFRAME** compounds found 58 potent inhibitors (IC50 <1 μM) of free-living amoebae, including **19 active against *N. fowleri***; 19 compounds killed *N. fowleri* in vitro **within 24 h** — faster than current drugs — including **HDAC inhibitors** (quisinostat, panobinostat, pracinostat, dacinostat, fimepinostat), **HSP90 inhibitors** (radicicol, NVP-HSP990), halofuginone, fumagillin, bardoxolone, solithromycin, and acriflavine (P 32970675). Natural products (e.g., *Pinus densiflora* leaf extract, IC50 62.3 μg/mL) are selectively amebicidal while sparing rat glial cells (P 38835258). None are yet approved for human PAM.
- **Personalized/experimental:** no approved targeted therapy. Pharmacogenomics not applicable (pathogen, not host-genome driven).

Suggested chemical/intervention ontology terms: CHEBI:2682 amphotericin B; CHEBI:75291 miltefosine; CHEBI:2955 azithromycin; CHEBI:46081 fluconazole; CHEBI:28077 rifampicin; NCIT therapeutic hypothermia; NCIT ventriculostomy/CSF shunt.

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13. Prevention

Prevention is primarily behavioral and environmental — there is no vaccine for human use.

- **Primary prevention: keep water out of the nose** during warm-freshwater activities; use **nose clips** or hold the nose when jumping/diving; avoid stirring up sediment in warm shallow water (CDC guidance).
- **Nasal irrigation & ablution safety:** use only **sterile, distilled, or previously boiled-and-cooled water** in neti pots / sinus-rinse devices, and for **religious ablution (wudu)** where tap water may be under-chlorinated (P 22919000 P 21291600).

- **Water-system control:** adequate **chlorination/disinfection** of pools and splash pads; proper design/operation of treated recreational water venues (P 40146665).
- **Secondary prevention:** clinician awareness for **early recognition** of PAM in meningoencephalitis with freshwater exposure → faster diagnosis/treatment (P 40146665). P 26582886
- **Public-health measures:** environmental water surveillance (PCR/LAMP), outbreak investigation, and public education in endemic/warm regions (P 25822175).
- **Immunization:** experimental **DNA vaccine against *nfa1*** induces protective Th1/Th2 immunity in mice — **no human vaccine** (P 22955499).

14. Other Species / Natural Disease

- **Agent taxonomy:** *Naegleria fowleri*, NCBI Taxon:5763 (Heterolobosea, Percolozoa).
- **Host range / experimental hosts: Mice** are the standard experimental host and develop a disease resembling human PAM after intranasal inoculation (P 646016). P 669800
- **Natural disease in cattle (*Bos taurus*, NCBI Taxon:9913):** A documented outbreak killed nine 10–20-month-old **Holstein heifers** in California (summers 1998–1999) that drank untreated warm surface water (>42 °C); autopsy showed **necrosuppurative hemorrhagic meningoencephalitis with olfactory lobes/nerves most severely affected**, N. fowleri confirmed by IHC and culture — "the disease in cattle closely resembles primary amoebic meningoencephalitis in humans" (P 16475525).

This establishes PAM as a genuine **naturally occurring** cross-species disease sharing route of entry, climate dependence, and pathology. Veterinary relevance: include *Naegleria* meningoencephalitis in summer bovine CNS differentials in hot regions.

- **Zoonotic potential: None in the classic sense** — not transmitted animal-to-human or human-to-human; acquisition is strictly **environmental** (waterborne via nose). (Rare iatrogenic concern: organ-transplant transmission from infected donors —

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P 24279908

- **Comparative biology:** non-pathogenic congener *N. gruberi* and related *Willaertia magna* share some virulence-gene homologs but lack full pathogenicity, enabling comparative virulence studies

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P 31797948

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P 33843581

15. Model Organisms

- **Mouse (BALB/c, others):** the principal in vivo model; **intranasal** inoculation reproduces olfactory-nerve invasion and lethal meningoencephalitis

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P 646016

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P 669800

Used to study innate (neutrophil) defense, protective immunity, passive immunization, and DNA vaccination

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P 2628288

P 2486833

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P 22955499

- *Phenotype recapitulation:* high — mirrors route of entry, CNS pathology, rapid lethality, and sex/age-dependent susceptibility (females and older mice more resistant;

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P 669800

- *Limitations:* dose/route differences (IV vs intranasal), accelerated course, and species differences in immune response.
- **In vitro / cellular models:** co-culture with **human fibrosarcoma cells**, MDCK epithelial cells, and primary nasal epithelial cells to dissect contact-dependent trogocytosis and EV-mediated cytopathy
  (P 40096149). P 40312759
- **Omics models:** axenic vs brain-passaged trophozoite proteomics/transcriptomics and secretome/EV proteomics for virulence-factor discovery
  (P 40096149 P 39735262). P 33843581
- **Resources:** ATCC strains of *N. fowleri*; CDC Free-Living and Intestinal Amebas Laboratory (surveillance, PCR, strain archiving).

Evidence Source Legend

Human clinical/epidemiologic:

P 32369575

P 26582886

P 42764041

P 41873284

P 40146665

P 27123690

P 23621053

P 22919000

P 23710088

P 35020127

P 25667249

P 26679626

P 27525348

P 24279908

P 21291600

P 39780139

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In vitro/mechanistic:

P 40096149

P 40312759

P 39432113

P 32716210

P 40016342

P 36839446

P 39735262

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Experimental therapeutics (in vitro/preclinical):

P 32970675

P 38835258

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Model organism (mouse):

P 646016

P 669800

P 2628288

P 2486833

P 22955499

Natural animal disease (veterinary):

P 16475525

Genomics/phylogenomics:

P 33843581

P 31797948

P 39826589

Supported vs Refuted Hypotheses

Supported: (1) PAM is a pathogen-caused infectious disease with **no human causal gene** (etiology = *N. fowleri*). (2) Exposure is overwhelmingly **warm-freshwater nasal entry** with olfactory-nerve CNS invasion. (3) Disease is **>95–97% fatal**, predominantly in **young males**. (4) Cytopathy is dual — **contact-dependent actin/food-cup trogocytosis** plus **contact-independent EV/pore-forming/protease cytolysis**. (5) **Non-recreational tap-water routes** (ablution, neti-pot) are real and epidemiologically important. (6) PAM occurs as a **natural cross-species disease** (cattle) and is well modeled in **intranasally-inoculated mice**. **Refuted / not applicable:** Any human Mendelian inheritance, susceptibility/protective loci, ClinVar variants, chromosomal abnormalities, genetic testing, carrier screening, or genetic counseling role — none exist for this infectious disease. Person-to-person and classic zoonotic animal-to-human transmission are **not** supported (acquisition is strictly environmental; rare iatrogenic transplant risk aside).

Limitations & Future Directions

Evidence is dominated by rare case reports and pooled surveillance (no RCTs; survivorship anecdotal). Optimal drug regimen and the independent contribution of hypothermia remain undefined. Priorities: validated early rapid diagnostics (point-of-care PCR/LAMP), new amebicidal drugs crossing the blood–brain barrier, and climate-driven surveillance as the amoeba's geographic range expands.
