Haemophilus Meningitis (MONDO:0000889): A Comprehensive Disease Characterization

Infectious Disease Knowledge Base Report — compiled from iterative literature synthesis (59 citations, 12 recorded findings)

Summary

Haemophilus meningitis (MONDO:0000889; ICD-10 **G00.0** "Haemophilus meningitis"; MeSH **D008586** "Meningitis, Haemophilus") is an acute bacterial (pyogenic) meningitis caused by the human-restricted Gram-negative coccobacillus *Haemophilus influenzae*, historically and predominantly serotype **b (Hib)**. It is an **infectious, non-genetic disease**: there is no causal human gene, no Mendelian inheritance, and no OMIM entry for the disease itself. The information base is aggregated disease-level epidemiology, clinical cohorts, randomized trials, and experimental animal/cell-barrier models rather than individual-patient genetic data.

The pathophysiology is a well-defined causal chain: the **polyribosylribitol phosphate (PRP) capsule** allows Hib to resist phagocytosis and complement, survive in the bloodstream, and invade the blood–CSF barrier in a polarized fashion; once in the subarachnoid space, shed **lipooligosaccharide (LOS)** triggers a **TNF-α / IL-1β-driven** meningeal inflammatory cascade that produces cerebral edema, raised intracranial pressure, cochlear injury, and neuronal damage. Clinically the disease presents with fever, headache, neck stiffness, photophobia and altered mental status; case fatality reaches up to ~30% and roughly 50% of survivors develop neurological sequelae (deafness, seizures, cognitive impairment, hydrocephalus). Treatment is a third-generation cephalosporin (ceftriaxone or cefotaxime) plus **adjunctive dexamethasone**, which reduces hearing loss with the strongest evidence in Hib meningitis when given before or with the first antibiotic dose.

The single most important fact about this disease in the modern era is the transformative impact of **PRP–protein conjugate vaccination**. Hib was the leading cause of childhood bacterial meningitis in the pre-vaccine era; conjugate vaccines drove incidence down by 96–

98% in surveillance settings. Residual and re-emerging disease is now driven by **non-b serotypes — notably *H. influenzae* type a (Hia) in Indigenous North American children** — as well as nontypeable strains and disease in older/comorbid adults. Meningitis overall remains a major global killer (GBD 2023: ~259,000 deaths, 2.54 million cases, >⅓ of deaths in children under 5), concentrated in low-income settings and the African meningitis belt.

Section 1 — Disease Information

Overview. Haemophilus meningitis is inflammation of the leptomeninges and subarachnoid CSF caused by *Haemophilus influenzae*, a fastidious Gram-negative coccobacillus that is an obligate human commensal/pathogen of the upper respiratory tract. Encapsulated strains (serotypes a–f, distinguished by capsular polysaccharide) cause invasive disease; **serotype b (Hib)** historically accounted for the overwhelming majority of meningitis cases. Prior to conjugate vaccination, "Hib was the leading cause of meningitis in children prior to the introduction of an effective vaccination" (PMID: 21999651).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0000889 (Haemophilus meningitis)
ICD-10	G00.0 (Haemophilus meningitis)
ICD-11	1D01.0 (Bacterial meningitis) / infectious meningitis codes
MeSH	D008586 "Meningitis, Haemophilus"
MeSH (organism)	D006193 "Haemophilus influenzae"
NCBI Taxonomy	*Haemophilus influenzae* — txid727
OMIM	Not applicable (infectious disease, no Mendelian gene)
Orphanet	Not a rare disease in the Orphanet sense (common infection)

Synonyms / alternative names. *Haemophilus influenzae* meningitis; Hib meningitis; *H. influenzae* type b meningitis; pyogenic/bacterial meningitis due to *H. influenzae*; historically "influenzal meningitis" (a misnomer from the erroneous 1890s belief that *H. influenzae* caused influenza).

Data source type. Aggregated, disease-level resources (national surveillance, clinical cohorts, RCTs, meta-analyses, experimental models). Not individual-patient EHR-derived and not genetic-variant-derived.

Section 2 — Etiology

Causal factor: infectious. The disease is caused by *Haemophilus influenzae*; it is not genetic and not environmental in origin, although host and environmental factors modulate susceptibility.

Risk factors (environmental / host): - **Age:** highest risk in infants and young children, especially 6–23 months; "Haemophilus influenzae type b (Hib) causes invasive infections almost exclusively in under-fives with those aged 6-23 months being the most vulnerable" (PMID: 38070126). Young age (<1 year) is an independent predictor of poor outcome (PMID: 34732790). - **Lack of vaccination / incomplete Hib immunization.** - **Immunocompromise:** asplenia, HIV, complement deficiency — high-risk groups for invasive encapsulated-bacterial disease (PMID: 36287171). - **CSF shunts / neurosurgical devices** (nosocomial/device-associated meningitis) (PMID: 40249832). - **Indigenous ethnicity (American Indian/Alaska Native)** — markedly elevated invasive *H. influenzae* risk: "Invasive Haemophilus influenzae type b (Hib) disease is a serious bacterial infection that disproportionally affects American Indian and Alaska Native (AI/AN) populations" (PMID: 39264849). - **Crowding / close-contact settings** (households, communities) facilitate transmission of nasopharyngeal carriage. - **Male sex** was an independent risk factor for poor outcome in shunt-associated pediatric meningitis (OR 2.82) (PMID: 40249832).

Genetic risk factors. No single causal or susceptibility gene is established. In an Amish Hib outbreak investigation, inbreeding was **not** a significant risk factor and cases shared no common HLA haplotype (PMID: 3485275) — arguing against a strong monogenic host susceptibility. Known immunodeficiencies (complement C2–C9, properdin, antibody deficiencies, asplenia) predispose broadly to encapsulated-organism invasive disease.

Protective factors. - **Anti-PRP antibody** (naturally acquired or vaccine-induced) is protective; the long-term protective threshold is ~1 µg/mL anti-PRP (PMID: 38070126). - **Hib conjugate vaccination** (primary protective intervention — see Sections 12–13). - Breastfeeding and herd immunity (reduced carriage) are recognized protective influences in the broader literature.

Gene–environment interactions. Not established for this infectious disease; the dominant "interaction" is between host immune status (age-dependent antibody repertoire, immunodeficiency) and pathogen exposure/carriage.

Section 3 — Phenotypes

Haemophilus meningitis produces the phenotypes of acute bacterial meningitis. The classic triad (fever, neck stiffness, altered mental status) is frequently incomplete: only ~26% show the full triad but ~83% have ≥2 of 4 cardinal features (PMID: 28879886).

Phenotype	Type	HPO suggestion	Onset/severity	Frequency
Fever	Clinical sign	HP:0001945	Acute, moderate–severe	Very frequent
Headache	Symptom	HP:0002315	Acute	Very frequent
Nuchal rigidity / meningismus	Clinical sign	HP:0031179	Acute	Frequent (can be subtle/absent early)
Photophobia	Symptom	HP:0000613	Acute	Frequent
Altered mental status / reduced consciousness	Clinical sign	HP:0001259 / HP:0001298	Acute	Frequent; GCS<13 predicts poor outcome
Seizures	Clinical sign	HP:0001250	Acute; may become chronic disorder	~10% (seizure disorder as sequela)
Sensorineural hearing loss	Lab/clinical	HP:0000407	Acute onset, often permanent	~14%
Subdural effusion	Physical/ imaging	HP:0012595	Acute	~23%
Hydrocephalus	Physical/ imaging	HP:0000238	Subacute	~6%
Developmental delay / cognitive impairment	Cognitive	HP:0001263 / HP:0100543	Long-term sequela	~9%
Focal motor deficit	Clinical sign	HP:0007360	Acute/long-term	Present in cohorts
CSF neutrophilic pleocytosis	Lab abnormality	HP:0012229	Acute	Near-universal

Per-complication frequencies are drawn from a predominantly-Hib pediatric cohort where "Complications occurred in 26% of the patients and included subdural effusion 23%, hearing loss 14%, seizure disorder 10%, developmental delay 9%, hydrocephalus 6%" (PMID: 9570646). Meningeal signs can be subtle early: a confirmed adult *H. influenzae* meningitis case presented with rapid hearing loss and initially absent neck stiffness (PMID: 40509725).

Quality-of-life impact. Permanent sensorineural deafness, epilepsy, motor deficits, and cognitive/developmental impairment substantially reduce QoL in survivors; ~50% of survivors develop neurological complications (PMID: 33807653).

Section 4 — Genetic / Molecular Information

Not applicable to host genetics. Haemophilus meningitis has **no causal human gene, no pathogenic germline/somatic variant, no modifier gene, no host epigenetic driver, and no chromosomal abnormality**. It is not a heritable disorder; there is no ClinVar/OMIM/HGMD entry for the disease.

The relevant "molecular genetics" are those of the **pathogen**: - **cap b locus (bexA–D and type-specific region)** encodes biosynthesis/export of the **PRP capsule** — the principal virulence determinant. "Its major virulence factor is the polyribosyl ribitol phosphate (PRP) polysaccharide capsule" (PMID: 34076491). - **Lipooligosaccharide (LOS)** biosynthesis genes — LOS (endotoxin) is the key inflammatory trigger. - **Fimbriae/pili and outer-membrane proteins** modulate adhesion and blood–CSF-barrier invasion (PMID: 30049648; PMID: 41318968). - **vapD/vapX toxin–antitoxin locus** enhances intracellular survival in epithelial and brain microvascular endothelial cells (PMID: 15274747).

Serotype is defined by capsular polysaccharide structure; molecular modeling shows serotype a and b capsular polysaccharides differ conformationally enough to lack cross-protective antibody recognition (PMID: 34491462) — relevant to serotype-replacement disease.

Section 5 — Environmental Information

Infectious agent (organism): *Haemophilus influenzae* (NCBI:txid727), serotype b predominant historically; serotypes a, e, f and nontypeable strains increasingly relevant. Transmission is person-to-person via respiratory droplets and nasopharyngeal carriage. Asymptomatic

nasopharyngeal carriage among healthcare workers and community members serves as a reservoir; carriage prevalence for *H. influenzae* was 11.8% among paediatric healthcare workers in Benin (none serotype b) (PMID: 40847276).

Environmental / lifestyle factors that increase transmission or susceptibility: crowding, daycare attendance, household exposure, tobacco smoke exposure, and lack of vaccination. There are no chemical toxins or occupational exposures that cause this disease. CHEBI-relevant molecular entities in pathogenesis: **lipopolysaccharide/lipooligosaccharide (CHEBI:16412)** and **PRP (ribitol phosphate polymer)**.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain

1. **Nasopharyngeal colonization** by encapsulated *H. influenzae* (usually Hib) **leads to** local mucosal adherence (fimbriae, OMPs) and, in susceptible hosts, mucosal invasion.
2. Mucosal invasion **results in bacteremia**; the **PRP capsule** confers resistance to phagocytosis and complement-mediated killing, **enabling** bloodstream survival and high-grade bacteremia. *(Demonstrated: capsule is the major virulence factor — [PMID: 34076491].)*
3. Sustained bacteremia **leads to** interaction with the **blood–CSF barrier** (choroid plexus epithelium) and blood–brain barrier (microvascular endothelium). Hib invades the barrier **in a polarized manner from the basolateral "blood" side** and/or by transcytosis. *(Demonstrated in HIBCPP cell model — [PMID: 30049648]; transcytosis inferred as a shared CNS-entry route — [PMID: 20026234].)*
4. Barrier penetration **results in** bacterial entry into the **subarachnoid space / CSF**, an immunologically permissive compartment with low complement and antibody.
5. Bacterial multiplication and **autolysis/LOS shedding trigger** release of **lipooligosaccharide (endotoxin)** into CSF.
6. LOS **induces** resident macrophages/microglia and meningeal cells to produce **TNF-α and IL-1β** — the seminal early cytokines. In the rabbit model TNF activity appears in CSF within 45 min of intracisternal LOS, **preceding** leukocyte influx by ~75 min. *(Demonstrated — [PMID: 2373990]; [PMID: 2794062].)*

7. TNF-α/IL-1β **cause** upregulation of endothelial adhesion molecules and chemokines, **leading to neutrophilic pleocytosis** (leukocyte influx into CSF). Combined TNF-α + IL-1β act **synergistically**. *(Demonstrated — [PMID: 2373990].)*
8. Neutrophil influx and inflammation **result in** blood–brain-barrier breakdown (increased permeability), **vasogenic and cytotoxic cerebral edema**, altered CSF dynamics, and **raised intracranial pressure**. In infant rats Hib causes greater BBB albumin penetration than other pathogens, correlating with CSF TNF ([PMID: 9184127]).
9. Edema + inflammation + vasculitis/thrombosis **branch into**:
10. **(a) Global injury:** raised ICP → reduced cerebral perfusion → **ischemia/hypoxia → neuronal necrosis/apoptosis** → coma, death.
11. **(b) Cochlear injury:** inflammation tracks along the cochlear aqueduct to the inner ear → **cochlear/eighth-nerve inflammation → sensorineural hearing loss**. *(Dexamethasone reduces cochlear-nerve inflammation in infant rats — [PMID: 1759817].)*
12. **(c) Local complications:** subdural effusion, hydrocephalus (impaired CSF resorption), seizures, focal deficits.
13. These processes **manifest clinically** as fever, meningismus, altered consciousness, seizures; and, in survivors, as **long-term sequelae** (deafness, epilepsy, cognitive impairment, hydrocephalus).

Detail by category

- **Molecular pathways:** LOS/LPS → TLR4/CD14 signaling → NF-κB activation → transcription of TNF-α, IL-1β, IL-6, chemokines (inferred canonical pathway; the cytokine outputs are directly demonstrated). Anti-inflammatory **IL-10** counter-regulates: intracisternal IL-10 >1 µg significantly reduced CSF TNF-α and lactate (PMID: 9359724).
- **Cellular processes:** acute inflammation, leukocyte recruitment, endothelial activation, apoptosis/necrosis of neurons, disruption of tight-junction proteins (occludin, claudins, JAMs) by bacterial virulence factors (PMID: 41318968).
- **Immune involvement:** innate immune over-activation drives injury; anti-PRP humoral immunity is protective. Specific cytokine inhibitors (sTNFR, IL-1RA) did **not** consistently modulate LOS-driven meningeal inflammation, suggesting redundancy/broad stimulus (PMID: 7798656).
- **Tissue damage mechanisms:** oxidative stress, ischemia (vasculitis/thrombosis), cytotoxic + vasogenic edema, elevated CSF lactate.

- **Suggested GO / CL / UBERON terms:** GO:0006954 inflammatory response; GO:0032640 tumor necrosis factor production; GO:0032611 IL-1β production; GO:0050900 leukocyte migration; GO:0006909 phagocytosis; CL:0000235 macrophage; CL:0000129 microglial cell; CL:0000775 neutrophil; CL:0002139 endothelial cell of vascular tree; CL:0000066 epithelial cell (choroid plexus); UBERON:0002361 meninges; UBERON:0001359 CSF; UBERON:0001886 choroid plexus.

Section 7 — Anatomical Structures Affected

- **Primary organ/system:** central nervous system — **meninges (UBERON:0002361)** and **subarachnoid space/CSF (UBERON:0001359)**; the **brain (UBERON:0000955)** is secondarily affected via edema, ischemia, and abscess/effusion.
- **Secondary organ involvement / complications: inner ear/cochlea (UBERON:0001844)** → deafness; **cerebral ventricles** → hydrocephalus; **subdural space** → subdural effusion/empyema; systemic sepsis may cause transient myocardial dysfunction (neurogenic stunned myocardium) — reported with *H. influenzae* CNS infection in children (PMID: 40751825).
- **Body systems:** nervous, immune, and (via bacteremia) cardiovascular/systemic.
- **Tissue/cell level: choroid plexus epithelium** and **brain microvascular endothelial cells** (barrier invasion sites); **meningeal macrophages/microglia** (cytokine production); **neutrophils** (CSF influx); **neurons** (injury); **cochlear hair cells / eighth cranial nerve** (hearing loss).
- **Subcellular:** endothelial/epithelial **tight junctions (GO:0005923 bicellular tight junction)**; plasma membrane signaling complexes (TLR4). Bacterial LOS acts at the cell surface.
- **Localization / lateralization:** the meningeal process is diffuse and **bilateral**; complications (subdural effusion, focal deficits, hearing loss) may be unilateral or asymmetric.

Section 8 — Temporal Development

- **Onset:** typically **acute** (hours to a few days); most common in **infants/young children** (peak 6–23 months). Adult cases occur, often in older/comorbid hosts.

- **Progression:** rapidly progressive if untreated; delays in diagnosis/treatment worsen outcome (PMID: 35419149). With effective antibiotics the acute illness is typically **self-limited over 7–14 days** of treatment; shorter (≤7 day) courses may be non-inferior for uncomplicated cases (PMID: 37870611).
- **Disease course:** monophasic acute illness (not relapsing/remitting), but with potential permanent sequelae. Critical intervention window: **early antibiotics + dexamethasone before/with the first antibiotic dose** is the key window to prevent hearing loss (PMID: 22789668).
- **Remission:** treatment-induced recovery in survivors; sequelae may be permanent.

Section 9 — Inheritance and Population

- **Inheritance: None — not a genetic disease** (no AD/AR/X-linked/mitochondrial pattern; not applicable).
- **Epidemiology (pre-vaccine):** Hib was the leading cause of childhood bacterial meningitis. In a Kuwait pediatric series *H. influenzae* accounted for 45.6% of bacterial meningitis episodes; 88% of cases were in children <5 years (PMID: 2607574).
- **Epidemiology (post-vaccine):** conjugate vaccines produced 96–98% reductions. Netherlands surveillance (1989–2019, 17,393 episodes): overall bacterial-meningitis incidence fell from 6.37 to 1.58 per 100,000/yr (IRR 0.25); Hib IRRs 0.02–0.04 (PMID: 33247582).
- **Current global burden:** GBD 2023 estimated 259,000 meningitis deaths and 2.54 million incident cases (all causes); children <5 accounted for >⅓ of deaths (86,600) (PMID: 41911930). An 80-year meta-analysis (371 studies, 157,656 episodes) found *H. influenzae* caused 22% of episodes with an identified pathogen and a case-fatality of 11% (95% CI 10–13%) — lower than pneumococcus (24%) or *Listeria* (27%) (PMID: 39093565).
- **Geographic distribution:** highest burden in low-income countries and the **African meningitis belt**; residual/re-emergent Hia disease concentrated in **Indigenous North American (Alaska Native, American Indian) children**.
- **Population demographics:** male predominance in some cohorts; strong age skew toward under-5s; ethnic disparity (AI/AN populations). Alaska Hia surveillance: average annual incidence 17.8/100,000 in children <5 vs 0.3 in ≥5 years (PMID: 40071574).

Section 10 — Diagnostics

- **Lumbar puncture / CSF analysis** is definitive. Bacterial meningitis CSF shows **neutrophilic pleocytosis, low glucose (hypoglycorrhachia), elevated protein**, elevated lactate, and elevated opening pressure.
- **Gram stain:** *H. influenzae* appears as **Gram-negative coccobacilli**.
- **Culture:** CSF and blood culture confirm the organism and enable **antimicrobial susceptibility testing** (essential given β-lactamase-mediated ampicillin resistance). Culture remains indispensable (PMID: 42256222).
- **Antigen detection:** latex agglutination for the PRP capsular antigen (adjunct, especially after antibiotic pretreatment).
- **Multiplex PCR (BioFire FilmArray Meningitis/Encephalitis panel):** detects 14 pathogens including *H. influenzae* directly from CSF in ~1 hour: "The FilmArray Meningitis/Encephalitis (ME) Panel provides multiplex molecular detection of 14 pathogens within ~1 h" (PMID: 42679643). In one evaluation, bacterial/fungal targets showed sensitivity 100%, specificity 94.9%, NPV 100% vs culture (PMID: 42388946). PCR markedly increases pathogen detection over culture in meningitis, particularly after antibiotic pretreatment (PMID: 40280145). Panels are adjuncts, not standalone replacements for culture (PMID: 42256222; PMID: 42684933).
- **Imaging:** CT/MRI to detect complications (subdural effusion, hydrocephalus, infarction, edema) and before LP if raised-ICP/mass concern.
- **Differential diagnosis:** pneumococcal and meningococcal meningitis (other pyogenic causes), viral/aseptic meningitis (lymphocytic pleocytosis, normal glucose — e.g., enteroviral [PMID: 41362530], drug-induced [PMID: 40827196]), tuberculous and cryptococcal meningitis ([PMID: 39998376]).
- **Genetic/omics testing: not applicable** for host diagnosis. Pathogen molecular typing (serotyping, WGS) is used for surveillance.

Section 11 — Outcome / Prognosis

- **Mortality:** case fatality up to ~30% for bacterial meningitis broadly (PMID: 33807653); *H. influenzae*-specific pooled case-fatality ~11% (PMID: 39093565), lower than pneumococcal disease.

- **Morbidity:** ~50% of survivors develop neurological complications (PMID: 33807653); sequelae include deafness, seizures, cognitive impairment, hydrocephalus, motor deficits.
- **Prognostic factors:** treatment setting/resources (Angola vs Finland OR 11.91), depressed consciousness (GCS<13, OR 4.58), seizures (OR 1.96), age <1 year (OR 1.55), and pneumococcal (vs Hib) etiology (PMID: 34732790). Dismal outcome (death/severe sequelae/deafness) occurred in 54% in Angola, 31% in Latin America, 5% in Finland — illustrating that outcome is dominated by setting and presenting severity.
- **Recovery:** with prompt appropriate therapy most survivors recover; permanent deficits (especially deafness) are the principal residual disability.

Section 12 — Treatment

Empiric antibiotics: third-generation cephalosporins — ceftriaxone or cefotaxime — are first-line (NCIT: Ceftriaxone C574; Cefotaxime C349). They are equivalent to conventional ampicillin-chloramphenicol in outcome where organisms are sensitive, but β-lactamase-producing Hib requires cephalosporins (PMID: 19375903). Where cephalosporins are unavailable, ampicillin–chloramphenicol is an alternative.

Adjunctive dexamethasone (NCIT: C459): reduces hearing loss and neurological sequelae, with the strongest, organism-specific benefit in Hib meningitis. Cochrane meta-analysis (25 RCTs, 4,121 participants): severe hearing loss RR 0.67 (95% CI 0.51–0.88), any hearing loss RR 0.74 (0.63–0.87), neurological sequelae RR 0.83 (0.69–1.00); mortality reduction non-significant (PMID: 20824838). Subgroup: corticosteroids "reduced severe hearing loss in Haemophilus influenzae meningitis (RR 0.34, 95% CI 0.20 to 0.59)" (PMID: 20824838). Benefit is clearest in high-income settings and requires timing **before or with the first antibiotic dose** (PMID: 22789668). Mechanistically, dexamethasone suppresses LOS-induced CSF TNF (PMID: 2794062).

Treatment duration: shorter (≤7 days) courses may be non-inferior to longer courses for uncomplicated childhood meningitis (PMID: 37870611).

Supportive care: ICU-level management of raised ICP, seizures, fluid/electrolyte balance (SIADH), and hemodynamic support; audiology follow-up and rehabilitation for sequelae. Experimental immunomodulation (IL-10) reduces CSF TNF in models but is not clinical (PMID: 9359724); specific cytokine inhibitors were ineffective in models (PMID: 7798656).

Pharmacogenomics / gene therapy / cell therapy / targeted-immunotherapy: not applicable to this infectious disease.

Section 13 — Prevention

Primary prevention — vaccination (the cornerstone). PRP–protein conjugate vaccines (PRP-T, PRP-OMP, HbOC) generate protective anti-PRP antibody. "As a result of widespread use of the vaccines, the incidence of Hib infections, and their associated morbidity and mortality, has fallen dramatically across the globe" (PMID: 34590133). Protective anti-PRP threshold ~1 µg/mL; seroprotection rates ~74% in a Nigerian cohort (PMID: 38070126). **NCIT: Haemophilus b Conjugate Vaccine (C1213).**

Tailored recommendations: ACIP (2024) preferentially recommends **PRP-OMP-containing Hib vaccine for American Indian/Alaska Native infants** due to higher invasive-disease risk and earlier disease onset (PMID: 39264849). A **serotype a (Hia) conjugate vaccine** is in development, motivated by serotype-replacement disease and lack of a/b cross-protection (PMID: 34491462).

Chemoprophylaxis: rifampin for close/household contacts controls transmission and secondary cases — an Amish Hib outbreak ended after rifampin prophylaxis was extended to all community members <15 years (PMID: 3485275). **NCIT: Rifampin (C777).**

Secondary/tertiary prevention: early LP, rapid empiric antibiotics, adjunctive dexamethasone to prevent sequelae; audiological screening; cochlear implantation for post-meningitic deafness; targeted vaccination of high-risk groups (asplenia, HIV, complement deficiency) (PMID: 36287171). WHO's **"Defeating meningitis by 2030"** roadmap frames the global prevention strategy (PMID: 39006487).

Section 14 — Other Species / Natural Disease

Haemophilus influenzae is **human-restricted**; there is no significant natural reservoir or naturally occurring *H. influenzae* meningitis in companion animals or wildlife. Related *Haemophilus/Glaesserella* species cause veterinary disease (e.g., *Glaesserella (Haemophilus) parasuis* causes Glässer's disease/meningitis in swine; *Avibacterium (Haemophilus) paragallinarum* in poultry), but these are distinct organisms. **Zoonotic potential: none** for *H. influenzae*. NCBI Taxonomy: *H. influenzae* txid727; humans *Homo sapiens* txid9606. VBO/breed: not applicable.

Section 15 — Model Organisms

- **Infant rat (principal in vivo model):** 5-day-old rats develop hematogenous Hib meningitis after intraperitoneal inoculation (10^4–10^5 CFU), with reproducible bacteremia, weight loss, lethargy, and mortality; "because adult animals will not reliably develop meningitis after intranasal or intraperitoneal challenge, infant animals are used" (PMID: 10470555). Anti-LPS inner-core mAb (MAHI 3) raised survival from 10–17% to 60–90% (PMID: 10623558). The model recapitulates BBB permeability changes (PMID: 9184127) and cochlear-nerve inflammation reducible by dexamethasone (PMID: 1759817).
- **Rabbit intracisternal LOS/Hib model:** dissects the cytokine cascade (TNF-α/IL-1β kinetics, IL-10/dexamethasone modulation) (PMID: 2373990; PMID: 2794062; PMID: 9359724).
- **Cell-barrier models:** human choroid plexus papilloma (HIBCPP) blood–CSF barrier model and human brain microvascular endothelial cells (HBMEC) model bacterial invasion, polarity, and tight-junction disruption (PMID: 30049648; PMID: 15274747; PMID: 41318968).

Recapitulation / limitations: models faithfully reproduce bacteremia→CNS invasion, cytokine-driven inflammation, BBB permeability, and cochlear injury, and were pivotal in validating adjunctive dexamethasone. Limitations: age-restriction (only infant animals), inoculum route differs from natural mucosal acquisition, and species differences in immune response.

Key Findings (with statistical evidence)

Finding 1 — Conjugate vaccines produced a dramatic global decline from Hib's pre-vaccine dominance

Hib was the single most common cause of childhood bacterial meningitis before vaccination. Netherlands national surveillance (1989–2019, 17,393 episodes) showed overall bacterial meningitis incidence fell from 6.37 to 1.58 per 100,000/yr (IRR 0.25, 95% CI 0.23–0.26; P<.001), with conjugate vaccines reducing Hib incidence at IRRs of 0.02–0.04 (P<.001): "Conjugate vaccines effectively reduced the incidence of Haemophilus influenzae type b… (IRRs, .02–.04; P < .001)" (PMID: 33247582); "the incidence of Hib infections… has fallen dramatically across the globe" (PMID: 34590133); "Hib was the leading cause of meningitis in children prior to the introduction of an effective vaccination" (PMID: 21999651).

Finding 2 — Pathophysiology is LOS-triggered, TNF-α/IL-1β-driven meningeal inflammation

In the rabbit model, intracisternal Hib LOS induced CSF TNF within 45 min, preceding leukocyte influx by ~75 min (peak TNF 45 ng/mL at 120 min); anti-TNF-α and anti-IL-1β reduced inflammation and the two cytokines were synergistic. "These data provide evidence for a seminal role of TNF-alpha and IL-1 beta in the initial events of meningeal inflammation" (PMID: 2373990). Dexamethasone before/with LOS inhibits CSF TNF: "DXM, when given before or with Hib LOS, inhibits CSF TNF production" (PMID: 2794062).

Finding 3 — Adjunctive dexamethasone reduces hearing loss, strongest in Hib

Cochrane meta-analysis (25 RCTs, 4,121 participants): severe hearing loss RR 0.67 (0.51–0.88), any hearing loss RR 0.74 (0.63–0.87), neurological sequelae RR 0.83 (0.69–1.00); mortality RR 0.90 (0.80–1.01, P=0.07, NS) (PMID: 20824838). Hib-specific benefit is greatest when dexamethasone is given before/with first antibiotic dose (PMID: 22789668).

Finding 4 — PRP capsule drives virulence; CNS entry is polarized barrier invasion

"Its major virulence factor is the polyribosyl ribitol phosphate (PRP) polysaccharide capsule" (PMID: 34076491). "Invasion occurs in a strongly polar fashion, since the bacteria enter the cells preferentially from the basolateral 'blood' side" (PMID: 30049648); transcytosis is a shared CNS-entry route (PMID: 20026234).

Finding 5 — Outcomes are dominated by setting and presenting severity

Pooled 5-trial analysis (2,123 children): dismal outcome in 54% (Angola), 31% (Latin America), 5% (Finland); independent predictors included study site (Angola vs Finland OR 11.91), GCS<13 (OR 4.58), seizures (OR 1.96), age <1 year (OR 1.55) (PMID: 34732790).

Finding 6 — Clinical presentation and complication frequencies

Case fatality up to 30%, ~50% of survivors with complications (PMID: 33807653); Saudi pediatric series (66% Hib): complications 26% — subdural effusion 23%, hearing loss 14%, seizure disorder 10%, developmental delay 9%, hydrocephalus 6% (PMID: 9570646); meningeal signs can be subtle early (PMID: 40509725).

Finding 7 — Infant rat is the principal in vivo model

Adult animals do not reliably develop meningitis (PMID: 10470555); infant-rat hematogenous model with anti-LPS protection (PMID: 10623558); Hib causes greater BBB penetration than E. coli K1 or GBS (PMID: 9184127).

Finding 8 — Rifampin chemoprophylaxis controls outbreaks

"The outbreak ended following rifampin prophylaxis of all community members younger than 15 years of age" (PMID: 3485275); inbreeding not a risk factor, no shared HLA haplotype.

Finding 9 — Meningitis is a leading infectious killer of young children

"meningitis, encephalitis and neonatal sepsis, collectively, [are] the second and third largest infectious killers of children under five" (PMID: 33668442).

Finding 10 — Diagnosis: LP/CSF + Gram/culture + multiplex PCR

FilmArray ME panel detects 14 pathogens including *H. influenzae* in ~1 h (PMID: 42679643); bacterial/fungal target sensitivity 100%, specificity 94.9%, NPV 100% vs culture (PMID: 42388946).

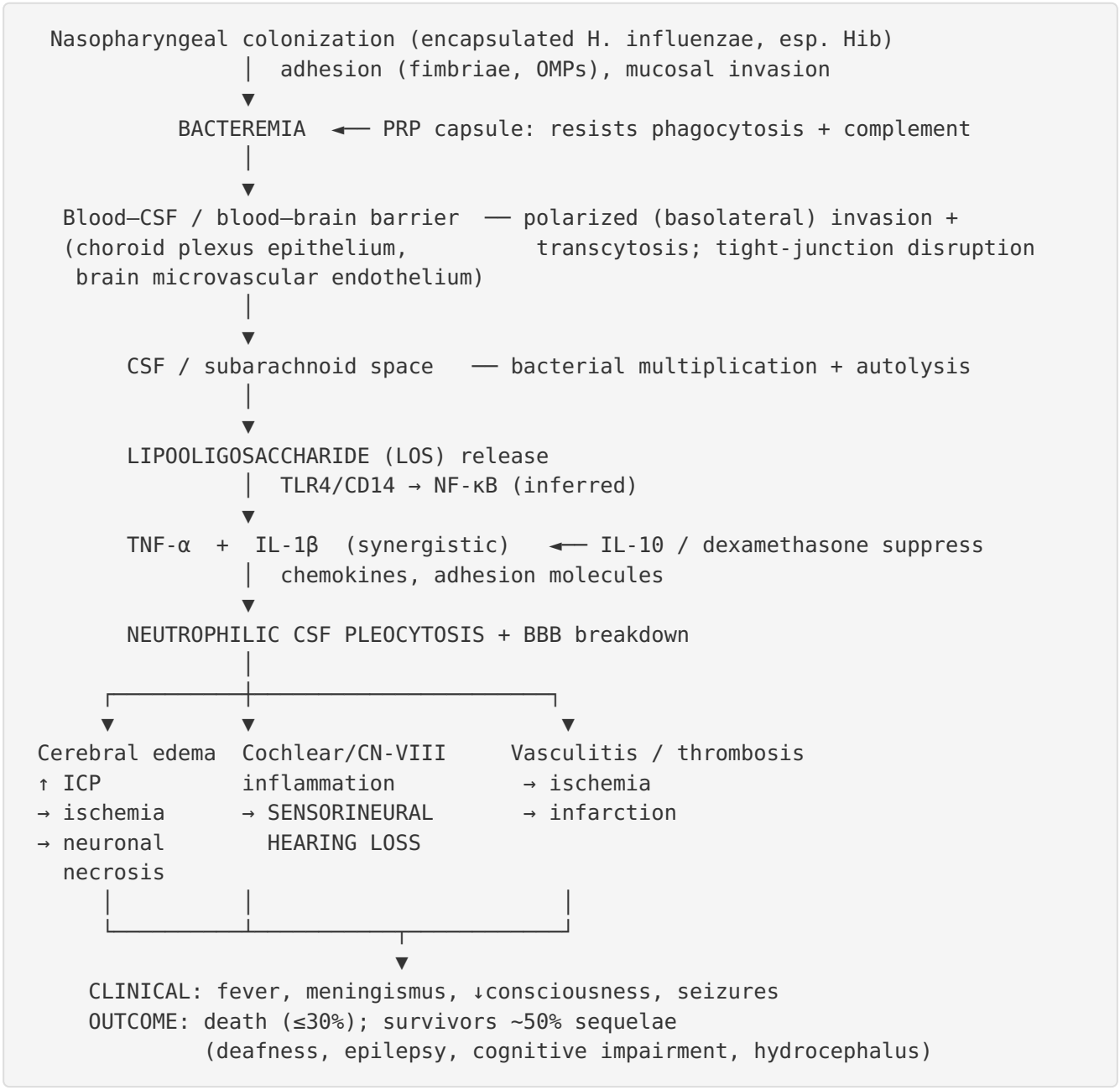
Finding 11 — Current global burden (GBD 2023)

"In 2023, there were 259 000 (202 000–335 000) global deaths and 2·54 million (2·20–2·93) incident cases of meningitis. Children younger than 5 years accounted for more than a third of deaths (86 600)" (PMID: 41911930); 80-year meta-analysis of case-fatality trends (PMID: 39093565).

Finding 12 — Serotype replacement: Hia now drives disease in Indigenous North American children

Alaska 2018–2022: 75% of 52 invasive Hia cases in Alaska Native children <5 in rural areas; incidence 17.8/100,000 in <5s (PMID: 40071574); "All deaths (n = 6) and long-term sequelae (n = 7) occurred in children with Hia or Hib meningitis" (PMID: 40882866); ACIP tailored PRP-OMP recommendation for AI/AN infants (PMID: 39264849).

Mechanistic Model / Interpretation



Upstream vs downstream. The **capsule** and **barrier invasion** are upstream determinants of *whether* invasive disease occurs; the **LOS→TNF-α/IL-1β cascade** is the upstream determinant of *how much injury* occurs once bacteria reach the CSF. This distinction explains why the two most effective interventions act at different points: **vaccination/anti-PRP antibody** blocks the upstream capsule-dependent step (prevention), while **dexamethasone** dampens the

downstream cytokine cascade (reduces sequelae, especially deafness). Antibiotics kill bacteria but, by causing bacteriolysis and LOS release, can transiently intensify the cytokine surge — the mechanistic rationale for giving dexamethasone *before or with* the first antibiotic dose.

Evidence Base

PMID	Contribution	Supports
33247582	30-yr Netherlands surveillance; conjugate-vaccine IRRs 0.02–0.04	F1 (vaccine impact)
34590133	Global dramatic Hib decline	F1, prevention
21999651	Hib as pre-vaccine leading cause	F1
2373990	TNF-α/IL-1β seminal role, rabbit model	F2 (mechanism)
2794062	Dexamethasone suppresses LOS-induced CSF TNF	F2, treatment
9359724	IL-10 counter-regulates CSF TNF	Mechanism
7798656	sTNFR/IL-1RA ineffective vs LOS (redundancy)	Mechanism nuance
20824838	Cochrane: dexamethasone RR 0.34 severe hearing loss in Hib	F3 (treatment)
22789668	Timing of dexamethasone in Hib	F3
34076491	PRP as major virulence factor	F4
30049648	Polarized blood–CSF invasion (HIBCPP)	F4, models
20026234	Transcytosis CNS entry	F4
41318968	Tight-junction disruption mechanisms	Mechanism/anatomy
15274747	vapD/vapX intracellular survival	Molecular
34732790	Prognostic factors, 3-continent outcomes	F5
33807653	Case fatality, complication spectrum	F6
9570646	Per-complication frequencies (66% Hib cohort)	F6
40509725	Subtle early meningeal signs, adult case	F6
10470555	Infant-animal model rationale	F7 (models)
10623558	Infant-rat model, anti-LPS protection	F7
9184127	BBB permeability greater with Hib	F7
1759817	Dexamethasone ↓ cochlear inflammation	F7, treatment
3485275	Rifampin controls Amish outbreak	F8 (prevention)

PMID	Contribution	Supports
33668442	Meningitis global mortality ranking	F9
42679643	FilmArray ME panel (14 pathogens, ~1h)	F10 (diagnostics)
42388946	ME panel performance vs culture	F10
42256222	Culture still essential (AST, coverage)	F10
41911930	GBD 2023 burden estimates	F11
39093565	80-yr case-fatality meta-analysis (H. flu 11%)	F11, prognosis
40071574	Alaska Hia epidemiology	F12
40882866	Hia/Hib drive deaths/sequelae in Alaska	F12
39264849	ACIP tailored AI/AN Hib vaccine	F12, prevention
34491462	a/b polysaccharide non-cross-reactivity	Serotype replacement
38070126	Seroprotection, ~1 µg/mL threshold	Prevention

Limitations and Knowledge Gaps

1. **Disease-level, not patient-level evidence.** This report synthesizes surveillance, cohorts, RCTs, and animal/cell models. There is no host-genetic dataset — appropriately, since the disease is infectious, not heritable. Sections 4 (host genetics), 14 (natural animal disease), and pharmacogenomics are largely "not applicable."
2. **Serotype-specific data are sparse for non-b strains.** Most mechanistic and much clinical data derive from Hib; the pathophysiology of Hia and nontypeable strains is assumed similar but less directly demonstrated.
3. **Corticosteroid benefit is setting-dependent.** Dexamethasone benefit is robust in high-income settings but not demonstrated in low-income countries where the disease burden is highest (PMID: 20824838) — a major equity gap.
4. **Signaling detail is partly inferred.** The TLR4/CD14→NF-κB step upstream of TNF-α/IL-1β is canonical/inferred; the cytokine outputs themselves are directly demonstrated in models.

5. **Model limitations.** Infant-rodent and rabbit models require non-natural inoculation routes and age restriction; they may not capture all aspects of human disease, particularly adult/comorbid presentations and long-term neurocognitive sequelae.
6. **Diagnostic gaps.** Multiplex PCR panels miss non-panel pathogens and cannot provide antimicrobial susceptibility; inter-platform discordance exists (PMID: 42684933). Culture remains essential.
7. **Surveillance heterogeneity.** Global burden estimates differ substantially between WHO-MCEE and IHME-GBD models (PMID: 33668442), reflecting under-diagnosis in low-resource settings.

Proposed Follow-up Experiments / Actions

1. **Accelerate Hia conjugate vaccine development and evaluation**, prioritizing Indigenous North American populations, given demonstrated serotype replacement, lack of a/b cross-protection, and concentrated mortality/sequelae (PMID: 34491462; PMID: 40071574; PMID: 40882866).
2. **Definitive RCTs of adjunctive dexamethasone (and alternative anti-inflammatories) in low-income, high-burden settings**, since current evidence of benefit is confined to high-income countries.
3. **Strengthen molecular surveillance** (serotyping + WGS) to track post-Hib serotype dynamics (a, e, f, nontypeable) and antimicrobial resistance, integrated with culture for AST.
4. **Mechanistic dissection of adjunctive host-directed therapies** beyond corticosteroids (e.g., targeted modulation of the LOS→TNF-α/IL-1β axis, complement or matrix-metalloproteinase modulation) using validated infant-rat and HIBCPP barrier models, focusing on hearing-loss and neuronal-injury endpoints.
5. **Improve early recognition tools** for atypical/subtle presentations (adults, subtle meningeal signs) to reduce diagnosis-to-treatment delays, which independently worsen outcome (PMID: 35419149).
6. **Standardize global burden estimation** by harmonizing WHO and GBD methodologies and expanding pathogen-specific surveillance in the African meningitis belt and other high-burden regions.

Report compiled from 12 confirmed findings and 59 literature citations across 5 investigation iterations. Evidence types span human clinical cohorts/RCTs/meta-analyses, model-organism (infant rat, rabbit) studies, in-vitro barrier models, and computational/molecular-modeling work.
