Acute bacterial meningitis

Emma C. Wall\textsuperscript{a,b}, Jia Mun Chan\textsuperscript{b}, Eliza Gil\textsuperscript{b}, and Robert S. Heyderman\textsuperscript{b}

\textbf{Purpose of review}
Community-acquired bacterial meningitis is a continually changing disease. This review summarises both dynamic epidemiology and emerging data on pathogenesis. Updated clinical guidelines are discussed, new agents undergoing clinical trials intended to reduce secondary brain damage are presented.

\textbf{Recent findings}
Conjugate vaccines are effective against serotype/serogroup-specific meningitis but vaccine escape variants are rising in prevalence. Meningitis occurs when bacteria evade mucosal and circulating immune responses and invade the brain; directly, or across the blood–brain barrier. Tissue damage is caused when host genetic susceptibility is exploited by bacterial virulence. The classical clinical triad of fever, neck stiffness and headache has poor diagnostic sensitivity, all guidelines reflect the necessity for a low index of suspicion and early Lumbar puncture. Unnecessary cranial imaging causes diagnostic delays. cerebrospinal fluid (CSF) culture and PCR are diagnostic, direct next-generation sequencing of CSF may revolutionise diagnostics. Administration of early antibiotics is essential to improve survival. Dexamethasone partially mitigates central nervous system inflammation in high-income settings. New agents in clinical trials include C5 inhibitors and daptomycin, data are expected in 2025.

\textbf{Summary}
Clinicians must remain vigilant for bacterial meningitis. Constantly changing epidemiology and emerging pathogenesis data are increasing the understanding of meningitis. Prospects for better treatments are forthcoming.

\textbf{Keywords}
antibiotics, dexamethasone, meningitis, pathogenesis, vaccines

\section*{INTRODUCTION}
Acute bacterial meningitis (ABM) is a disease with rapid onset, outbreak and epidemic potential, and high rates of mortality and morbidity [1,2]. Considerable advances have been made in the last 30 years towards epidemic management and disease control through vaccination, and understanding the contributions of both host and pathogen to clinical outcomes. In this review, we will summarise the rapidly changing epidemiology of ABM in the context of new vaccines. We will show how new unbiased genomics technologies are revealing specific host–pathogen interactions that cause inflammation and brain damage. Additionally, we will summarise which new adjunctive treatments are in development and describe how the current Severe Acute Respiratory Syndrome CoronaVirus2 (SARS-CoV2) pandemic may impact on the WHO’s efforts to defeat meningitis by 2030.

\section*{Epidemiology and impact of vaccination}
Community-acquired bacterial meningitis is predominately caused by three pathogens, \textit{Streptococcus pneumoniae}, \textit{Neisseria meningitidis} and \textit{Haemophilus influenzae} type B. Additionally, \textit{Streptococcus suis} in Southeast Asia, \textit{Listeria monocytogenes}, Group B \textit{Streptococci}, and Gram-negative bacteria such as \textit{Escherichia coli} and \textit{Klebsiella pneumoniae}, cause meningitis in specific groups, including neonates, pregnant women, transplant recipients and older adults [3]. Worldwide, the number of reported cases of bacterial meningitis to global surveillance sites rose between 2006 and 2016, with incidence strongly
**KEY POINTS**

- The epidemiology of bacterial meningitis is regional and highly dynamic, influenced by vaccines, climate, latitude, population movement, viral infections and poverty.
- Serotype/serogroup specific conjugate vaccines are highly effective in preventing meningitis, but serotype replacement is increasing, effectively limiting the impact of conjugate vaccines on disease incidence.
- Host and pathogen factors influence clinical outcomes, host genetic susceptibility to poor outcome from pneumococcal meningitis is linked to genes involved in NF-κB signalling and endothelial integrity.
- Dexamethasone improves outcome in pneumococcal meningitis in high-income settings only, new agents targeted at the host response are currently in clinical trials.

related to poverty (SDI) [3]. However, the geographical incidence varies significantly. In well-resourced settings, ABM incidence has fallen to below 0.5–1.5/100,000 population [4,5,6]. Contrastingly, in countries in the African Sahel region, where epidemic meningitis due to *N. meningitidis* and *S. pneumoniae* persists, incidence reaches 1000/100,000 cases [3,7–9]. Beyond the meningitis belt, the incidence in Africa approaches 2.5–25/100,000 per population [10,11].

Bacterial meningitis is globally associated with cooler, drier seasons [9]. It is likely that climate change will impact on meningitis incidence but modelling data are lacking [11]. Social distancing measures introduced to mitigate the spread of SARS-CoV2 during the CoronaVirus Infectious Diseases 2019 pandemic are also predicted to lead to a 20–30% decrease in meningitis incidence [12,13].

Global meningitis epidemiology is highly dynamic; changes in the last 25 years amongst adults and children have been influenced by the widespread use of conjugate vaccines [14–16], the HIV-1 epidemic [17–19], the roll-out of antiretroviral and antibacterial treatment including prevention of mother-to-child transmission [20,21], and significant progress on development and poverty reduction strategies (SDG), including improved maternal and neonatal care [22].

Vaccination remains the most important pillar of the WHO-led roadmap towards defeating meningitis by 2030 [23]. A summary of all available vaccines against the three common pathogens is given in Table 1.

**Streptococcus pneumoniae**

*S. pneumoniae* is the commonest cause of ABM worldwide. Reports of reduction in paediatric invasive pneumococcal disease (IPD), following pneumococcal conjugate vaccine introduction in higher-income countries, were rapidly followed by evidence of herd immunity in the wider adult population, particularly the elderly [24–26]. Incidence of *S. pneumoniae* meningitis is estimated to have fallen by 48% in children [14,16,27]. However, parallel reports have emerged of IPD, including meningitis, caused by nonvaccine serotypes [14,28–30]. To mitigate against serotype replacement and better prevent meningitis, new approaches to pneumococcal vaccine design are under development, including whole capsule and protein vaccines [31–34,35*].

**Neisseria meningitidis**

Conjugate meningococcal vaccines are highly effective in preventing meningitis caused by individual serogroups. Serogroup C incidence has declined dramatically following the introduction of Men-C vaccine in children in many high-income countries [36–38]. Epidemic meningitis caused by serogroup A in the Sahel region of Africa has been dramatically reduced by low-cost MenAfriVac serogroup A conjugate vaccine by 92% [39,40]. However, virulent clones of other serogroups have subsequently emerged (C, W, X) and epidemics of meningococcal meningitis continue to occur in the Sahel [41,42].

As serogroup C disease declined, serogroup B emerged as the leading cause of meningococcal meningitis in high SDI countries [15]. In 2015, the UK government introduced protein-based serogroup B vaccine 4CMenB (Bexsero) to all children under 2 years. UK cases of invasive serogroup B in children have declined 75% with an estimated overall vaccine efficacy of 54% [43]. However, disease due to other serogroups including W and Y remains problematic. MenC conjugate vaccine has now been replaced with quadrivalent MenACWY vaccine for all teenagers and young adults in the UK [38].

**Haemophilus influenzae**

Hib vaccination in 1989 led to dramatic reductions in paediatric meningitis between 75 and 95% [44,45]. Subsequently, Hib meningitis has virtually been eliminated globally in countries with effective Expanded Programme of Immunisations (EPI), but persists where vaccination coverage is poor including India, Nigeria, Pakistan and the Democratic Republic of Congo [16,44,46,47]. Hib conjugate vaccines are estimated to have reduced Hib meningitis by 49% globally 2000–2016 [3], and paediatric
deaths by 90% over the same time period [16]. However, it is concerning that non-type b stains such as Hia are emerging [42].

**Group B Streptococcus**

*Streptococcus agalactiae* (Group B Streptococcus, GBS) primarily causes meningitis in neonates but also causes sepsis in older adults with co-morbidities and young adults who have consumed contaminated fish [48]. Serotypes Ia, Ib, II, III and V account for 98% of human carriage serotypes isolated globally [49]. Clonal complex 17 (CC17) strains have been shown to be hypervirulent, accounting for more than 80% of the disease [50,51]. GBS disease-causing lineages have distinct niche adaptation and virulence characteristics [52,53]. The most promising strategy to eliminate neonatal meningitis caused by GBS is vaccination in pregnancy, trials are ongoing [54–57].

**PATHOGENESIS**

The pathogenesis of most ABM follows a sequential pattern: nasopharyngeal colonization, bloodstream invasion across the mucosa, circulation of bacteria to the central nervous system (CNS), and subsequent CNS entry [58*,59]. In ABM caused by *L. monocytogenes*, GBS and *S. suis*, bacteraemia has a gastrointestinal or genitourinary tract source [52,60,61]. Occasionally, ABM is acquired through direct CNS invasion through the cribriform plate [62,63]. In the majority of immunocompetent individuals, colonisation of the nasopharynx by *S. pneumoniae* and *N. meningitidis* is cleared by mucosal immunity, despite epithelial invasion [58*,59]. Co-infection with *S. pneumoniae* and respiratory viruses such as influenza causes a heightened inflammatory state associated with both pneumococcal and meningococcal invasion [64–66], indeed preceding influenza is associated with seasonal ABM [11,67*].

Bacteraemia usually precedes translocation across the blood–brain barrier (BBB) and/or blood–cerebrospinal fluid barrier into the CNS. Under basal conditions, the CNS environment is under continuous immunological surveillance [68]. This is achieved through the complexity of the BBB, where pericytes, astrocytes, microglia and specialised endothelial cells work in synergy

---

Table 1. Currently available vaccinations against meningitis-pathogens

| Vaccine formulation          | Vaccine name     | Serotypes covered | Protein conjugate | Commercially available vaccine          |
|-----------------------------|------------------|-------------------|-------------------|----------------------------------------|
| *Streptococcus pneumoniae*  |                  |                   |                   |                                        |
| Polysaccharide              | PPV-23           | 1, 2, 3, 4, 5, 6B, 7F, 8, 9V, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F | NA             | Pneumovax                              |
| Conjugate                   | PCV-7            | 4, 6B, 9V, 14, 18C, 19F, 23F | CRM197*         | Prevenar                               |
| Conjugate                   | PCV-10           | 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F | Protein D, diphtheria toxoid, tetanus toxoid | Synflorex                              |
| Conjugate                   | PCV-10           | 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F | CRM197         | Pneumosil                              |
| Conjugate                   | PCV-13           | 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F | CRM197         | Prevenar 13                            |
| *Neisseria meningitidis*    |                  |                   |                   |                                        |
| Conjugate                   | MenACWY          | ACWY              | CRM197, diphtheria toxoid | Menactra, Menveo Serum Institute of India (in development) |
| Polysaccharide              | MPSV4            | ACWY              | NA               | Menimmune                              |
| Conjugate                   | MenC             | C                 | CRM197 or tetanus toxoid | Menitorix, NeisVac-C, Menjugate, Meningitec |
| Conjugate                   | Hib_MenCY-TT     | CY, Hib           | Tetanus toxoid   | MenHibrix                              |
| Conjugate                   | Men A            | A                 | Tetanus toxoid   | MenAfriVac                              |
| Protein                     | Men B bivalent vaccine | B             | Not used         | Trumemba                                |
| Protein                     | 4CMenB           | B                 | Not used         | Bexsero                                 |
| *Haemophilus influenzae*    |                  |                   |                   |                                        |
| Conjugate                   | Monovalent       | Type b            | CRM197           | Menitorix, Pediacie                      |

*CRM197* = nontoxic variant of diphtheria toxin.
NA, Not available; PCV, Pneumococcal Conjugate Vaccine; PPV, Pneumococcal Polysaccharide Vaccine.
to both resist pathogen invasion and kill bacteria on entry [68] (Fig. 1). Bacteria breach the BBB by interacting with laminin receptors and exploiting endocytic pathways, for example via Platelet Activating Factor Receptor signalling [69–72] (Fig. 1). However, mechanisms by which ABM-causing bacteria subvert CNS barriers to cause meningitis are not fully described.

In the 10–30% of ABM cases without concurrent bacteraemia [73], bacteria may interact with gangliosides, adhere to the olfactory bulb, invade the olfactory epithelium and directly translocate to the brain [63,74–77]. Pneumococcal strains causing nonhematogenous meningitis tend to be less frequently studied using bacteraemia-based animal models [75–77].

**Inflammation and exacerbation of tissue damage in acute bacterial meningitis**

Bacteria replicate rapidly in the relatively immune-privileged CNS compartment [78], releasing Pathogen Associated Molecular Pattern (PAMP) s that bind to toll-like receptors including 2,3,4 and 9, triggering the release of Damage-Accociated Molecular Pattern Signallings (DAMPs) via Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) activation [79–82]. The subsequent release of extracellular cytokines and chemokines including Chemokine family Ligand 8 and cerebrospinal fluid (CSF)-3 drives a rapid influx of neutrophils to the CSF compartment [83**,**84].

Bacterial PAMPs and virulence proteins exert direct damage on the delicate structures of the CNS. Pneumococcal virulence factors, including capsule and pneumolysin, reduce microglia motility and chemotaxis [85*]. Pneumolysin, a cytolytic and Toll Like Receptor 4 agonist is implicated in directly toxic effects on host cells, particularly within the BBB and hippocampus [86,87]. Others stimulate CERB binding protein (CBP) and receptor for advanced glycation end products (RAGE), increasing Tumour Necrosis Factor alpha (TNF-α) levels and promoting BBB disruption [88,89*].
Host-detection of bacteria within the CNS triggers a highly inflammatory, and predominately ineffective host response, associated with further tissue damage. Sustained inflammation exacerbates tissue damage, leading to death or irreversible neurological damage [73,90,91]. Neutrophil infiltration is important for bacterial elimination [92]. However, neutrophils can directly damage the CNS [93]. Neutrophil extracellular traps (NETs) unexpectedly impaired CNS pneumococcal clearance and increased inflammatory damage in an experimental model [83**]. Damaging DAMPs released both from neutrophil degranulation and NF-κB signalling include myeloperoxidase, matrix-metalloproteinases, TNF-α and prostaglandins [94*,95,96,97*]. Neutrophil-mediated inflammation is strongly associated with dysfunctional coagulation and fibrinolytic cascade in the CNS, including an excess of the anaphylatoxin complement C5 [98].

Clinical improvement with dexamethasone adjunctive therapy in both Hib and pneumococcal meningitis demonstrates the importance of host-mediated inflammation in ABM [99,100]. Dexamethasone may reduce NF-κB signalling and cytokine release [101].

**Leveraging new technology to interrogate acute bacterial meningitis pathogenesis**

Bacterial genome-wide association studies (GWAS) have revealed loci that are implicated in invasiveness, tissue tropism and the ability to cause CNS disease [102**,103**,104,105]. Single Nucleotide Polymorphisms (SNPs) in the raf operon determine pneumococcal tropism for ear/brain or lungs in an intranasal challenge model [106*,107]. Additionally, SNPs in raf modulated neutrophil recruitment, leading to strain-dependent clearance [106*].

Gene expression in *S. pneumoniae* is niche dependent, highlighting the importance of bacterial metabolism in pathogenesis [108,109**]. In a quantitative proteomics study of ABM, the abundance of pneumococcal protein Elongation Factor Tu in CSF associated with severity in human disease [97*]. In a murine model, proteins AliB and competence peptides were implicated in pathogenesis [110]. Joint human–pathogen GWAS studies of meningitis patients suggest that genetic differences in the host response exert greater effects on susceptibility and disease severity than bacterial genotype. This GWAS identified variants in the *CCDC3* gene associated with disease severity [102**]. *CCDC3* is a multifunction gene involved in the metabolism and suppression of NF-κB–TNFα activation in endothelial cells [111].

### NEW DIRECTIONS IN DIAGNOSTICS AND CLINICAL MANAGEMENT

Early recognition and initiation of appropriate antimicrobials are essential to minimise death and complications from ABM. The differential diagnosis in patients presenting with headache, fever, neck stiffness or altered mental state is broad: the classical meningitis triad has limited diagnostic sensitivity [112]. A high index of clinical suspicion is thus required to diagnose ABM [113]. Lumbar puncture is essential, and should be undertaken promptly before CSF is rendered sterile by broad-spectrum antibiotics [114].

Many patients with ABM present with an altered level of consciousness, leading clinicians to frequently request cranial imaging prior to diagnostic lumbar puncture. Early Lumbar puncture (LP) is strongly associated with higher diagnostic yield from the CSF; delays in LP for cranial imaging lead to substantial reductions in yield in either CSF bacterial culture or PCR [114]. Delays to diagnosis are linked to worse clinical outcomes [114–116]. Cranial imaging (either CT or MRI) in patients with clear clinical signs and symptoms of meningitis without focal neurology is thus not recommended in the majority of patients with suspected ABM [117,118]. CT has poor inter-reporting reliability to predict the risk of cerebral herniation in ABM [119]. The American, British and European infection societies meningitis guidelines all recommend immediate LP in cases of suspected ABM without delay for CT/MRI in immunocompetent adults with suspected ABM who have a stable GCS of ≥12/15 without seizures [119–123]. Important contraindications to LP include shock, respiratory compromise, or coagulopathy.

The diagnosis of ABM is dependent on the analysis of CSF. The leukocyte count remains the strongest predictive value of ABM. Diagnostic models including clinical, CSF and blood data show little additional benefit beyond clinical judgement [111]. Antibiotic administration prior to LP commonly renders the CSF sterile, thus clinicians are increasingly dependent on diagnostic PCR. Recent data suggest that while small multiplex panels targeting Hib, meningococci and pneumococci are highly sensitive and specific [123], larger panels that include viral, nosocomial and rarer community-acquired pathogens have varying sensitivity and specificity and are not currently recommended [124]. More recently, direct next-generation sequencing (NGS) and metagenomics of CSF have been proposed to detect pathogens in cases with a high index of clinical suspicion of ABM but negative PCR tests [125**]. While this approach is promising,
constraints around cost, bioinformatics expertise and clinically relevant turnaround times have limited clinical use of NGS to date [124].

All guidelines recommend patients with suspected ABM should receive parenteral antibiotics within 1 h. However, only 46% of patients in a clinical research study were reported to meet this target, limited by delays in the emergency department [126,127]. Antibiotic choice should be determined by patient risk group, patient allergies, and local guidelines informed by epidemiology, including antimicrobial resistance. Penicillin resistance in S. pneumoniae is 15–20% in some settings, but remains <5% in N. meningitidis [128,129]. However, quinolone resistance in N. meningitidis reaches 70% in Southeast Asia [15,130]. Diagnostic uncertainty in culture-negative meningitis often leads to prolonged dual antibiotic and antiviral therapies, which may be associated with nosocomial complications [114,131*].

**Adjunctive therapies**

Adjunctive treatments are designed to reduce secondary inflammation in ABM and decrease the morbidity associated with CNS tissue damage. Inflammation is associated with secondary complications of ABM, including death, deafness, stroke, epilepsy and learning difficulties [91,131*,132–134]. Delayed cerebral thrombosis is a rare complication of ABM that can occur up to 2 weeks post-admission [135,136].

In hospitals in high-income settings, patients presenting with suspected pneumococcal meningitis should receive adjunctive dexamethasone to reduce mortality [90,137]. In low-income settings, dexamethasone is only indicated in cases of suspected S. suis meningitis in Southeast Asia to reduce deafness [137,138]. In other settings, particularly in Low and Middle Income Countries in Africa, dexamethasone is ineffective and should not be given [139].

Other previously tested adjuncts, including hypothermia and glycerol, have been shown to be potentially harmful and should not be administered [140,141].

**Emerging therapeutic targets**

Empirical antibiotic treatment in most centres for suspected ABM is the third-generation cephalosporin, ceftiraxone [92]. However, bacterial lysis by ceftiraxone releases DAMPs that may prolong damaging inflammation even as bacteria killed [88]. Research in animal models has strongly suggested bacteriostatic antibiotics are associated with less CNS inflammation and improve outcomes [142]. In clinical practice, there are little data to suggest different clinical outcomes occur between bacteriostatic vs. bactericidal antibiotics [143]. As such, there are continued efforts to develop alternatives that reduce sequelae in survivors. A phase 2 clinical trial evaluating the adjunctive use of a nonlytic antibiotic, daptomycin, for pneumococcal meningitis is currently underway (ClinicalTrials.gov identifier NCT03480191). Adjunctive administration of daptomycin may dampen the inflammatory effects of ceftiraxone through currently unknown mechanisms [144].

The damaging coagulation and fibrinolytic cascade in CSF are triggered partly by excess complement C5 [98]. Inhibition of C5 improved outcomes in a murine model, clinical trials of C5 antagonists are currently underway [145].

Newer therapeutic agents with intriguing survival data in animal models are not yet in clinical trials. These include DNase-1, targeted at disrupting ineffective NETosis, the possible neuroprotective effects of metformin, and matrix-metalloproteinase inhibitors targeted on preventing enzymatic tissue breakdown [83*,146–148]. Proposed adjunctive antipneumococcal therapy includes targeting pneumolysin and P4, a pneumococcal peptide that may inhibit replication [149,150].

**CONCLUSION**

Community-acquired bacterial meningitis presents ongoing formidable epidemiological and clinical challenges. The ability of meningitis-causing pathogens to evolve in the ecological niche of the nasopharynx during carriage, and escape serotype-specific vaccines has led to new strategies to eliminate disease carriage through serotype-independent vaccination. The outcome of CNS host-pathogen interactions determines clinical sequelae, influenced by host genetic susceptibility.

CSF analysis is essential to make a diagnosis of ABM, leukocyte count remains the most effective predictor of ABM over newer models. Nonindicated cranial imaging introduces significant diagnostic delays. Multiplex PCR panels have increasing utility in ABM diagnostics, however NGS remains a research tool.

Patients with ABM continue to experience significant complications, including death, stroke and deafness. Adjunctive dexamethasone improves survival in high-income countries only, the results of clinical trials of more targeted approaches are awaited. Effective and affordable, pan-serogroup vaccination remains a crucial goal if we are to eliminate this devastating disease.
CNS inflammatory disorders: infectious diseases

Acknowledgements

Financial support and sponsorship

E.W. is supported by a postdoctoral clinical research fellowship from the Francis Crick Institute, and the National Institute for Health Research University College London Hospitals Department of Health’s NIHR Biomedical Research Centre. E.C. and R.H. are funded by the National Institute for Health Research (NIHR) (project reference 16/136/46) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK government.

E.C and R.H are funded by the Medical Research Council grant number MR/T016329/1 and the National Institute for Health Research (NIHR) (project reference 16/136/46) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK government.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of outstanding interest

1. Lorton F, Chalumeau M, Assathiany R, et al. Vaccine-preventable severe morbidity and mortality caused by meningococcal and pneumococcal: a population-based study in France. Paediatr Perinat Epidemiol 2018; 32:442–447.

2. Boedhia NP, Schlapbach LJ, Dresen GI, et al. Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infections Disease Study (ECLUIDS). Crit Care 2018; 22:143. doi: 10.1186/s13054-018-2052-7.

3. Collaborators GBDM. Global, regional, and national burden of meningitis, 1999–2019: a systematic analysis for the Global Burden of Disease Study. Lancet Neurol 2018; 17:1061–1082.

4. Erdem H, Inan A, Guven E, et al. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis 2017; 36:1595–1611.

5. Hasbun R, Rosenthal N, Balada-Llasat JM, et al. Epidemiology of meningitis and encephalitis in the United States, 2011–2014. Clin Infect Dis 2017; 65:359–363.

6. Koelma DLH, van Kassel MN, Bijlsma MW, et al. Changing epidemiology of bacterial meningitis since introduction of conjugate vaccines: three decades of national meningitis surveillance in The Netherlands. Clin Infect Dis 2020. doi: 10.1093/cia/ciaa1774. Online ahead of print.

Updated European meningitis epidemiology showing S. pneumoniae meningitis increasing in adults in Europe.

7. Daugla DM, Gami JP, Gamoukam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PRa-ATT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. Lancet 2014; 383:40–47.

8. Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. BMC Infect Dis 2010; 10:22. doi: 1471-2334-10-22.

9. Paireau J, Chen A, Brouth H, et al. Seasonal dynamics of bacterial meningitis: a time-series analysis. Lancet Glob Health 2016; 4; e370–e377.

10. Wall EC, Everett DB, Mukama M, et al. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and Haemophilus influenzae type b vaccination, 2000–2012. Clin Infect Dis 2014; 58:e137–e145.

11. Mazamay S, Brouin H, Bompangue D. The environmental drivers of bacterial meningitis epidemics in the Democratic Republic of Congo, central Africa. PLoS Negl Trop Dis 2020; 14:e0008634. doi: 10.1371/journal.pntd.0008634.

12. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of invasive pneumococcal disease (IPD) caused by emerging serotypes after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in England; prospective observational cohort study, 2014–18. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa043. Online ahead of print.

Landmark data from the UK showing nonvaccine serotypes cause more severe IPD.

13. Luciani L, Ninove L, Zandotti C, Nougairede A. COVID-19 pandemic and its consequences disrupt epidemiology of enterovirus meningitis, South-East France. J Med Virol 2021; 93:1929–1931.

14. Oligbu G, Collins S, Djennad A, et al. Effect of pneumococcal conjugate vaccines on pneumococcal meningitis, England and Wales, July 1, 2000–June 30, 2016. Emerg Infect Dis 2019; 25:1708–1718.

15. Acedero R, Bai X, Borrow R, et al. The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: epidemiology, surveillance, hypervarient strains, antibiotic resistance and high-risk populations. Expert Rev Vaccines 2019; 18:15–30.

16. Wahl B, O’Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Lancet Glob Health 2018; 6:e744–e757.

17. Gianetti AR, Parawir I, Wosakana R, et al. The effect of HIV infection on adult meningitis in Indonesia: a prospective cohort study. AIDS 2009; 23:2309–2316.

18. Schutte CM, Van der Meyden CH, Magasi DS. The impact of HIV on meningitis as seen at a South African Academic Hospital (1994 to 1998), Infection 2000; 28:3–7.

19. van Aalst M, Lotsch F, Spijker R, et al. Incidence of invasive pneumococcal disease in immunocompromised patients: a systematic review and meta-analysis. Travel Med Infect Dis 2018; 24:89–100.

20. Hasperhoven GF, Al-Nasiry S, Bekker V, et al. Universal screening versus risk-based protocols for antibiotic prophylaxis during childbirth to prevent early-onset group B streptococcal disease: a systematic review and meta-analysis. BJOG 2020; 127:880–891.

21. Murray CI, Orthlad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study. Lancet 2014; 384:1005–1070.

22. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the sustainable development goals. Lancet 2016; 388:3027–3035.

23. WHO. Defeating bacterial meningitis by 2030. 2020. Available from: https://www.who.int/emergencies/diseases/meningitis-meningsitis-2030.pdf. [Accessed January 2021].

24. Harboe ZD, Dalby T, Weinerberger DM, et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clin Infect Dis 2014; 59:1056–1073.

25. Bijlsma MW, Brouwer MC, Kassemank ES, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. Lancet Infect Dis 2016; 16:339–347.

26. Lanquet G, Krizova P, Valentiner-Branth P, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. Thorax 2019; 74:492–492.

27. Ouldali N, Levy C, Varon E, et al. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. Lancet Infect Dis 2018; 18:983–991.

28. Koelma DLH, Brouwer MC, van de Beeck D. Resurgence of pneumococcal meningitis in Europe and Northern America. Clin Microbiol Infect 2020; 26:199–204.

29. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in nonvaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infect Dis 2018; 18:441–451.

30. Ciruela F, Izquierdo C, Broner S, et al. The changing epidemiology of invasive pneumococcal disease after PCV13 vaccination in a country with intermediate vaccination coverage. Vaccine 2018; 36:7744–7752.

31. Odutola A, Ota MOCC, Antonio M, et al. Efficacy of a novel, protein-based pneumococcal vaccine against nasopharyngeal carriage of Streptococcus pneumoniae in infants: a phase 2, randomized, controlled, observer-blind study. Vaccine 2017; 35:2531–2542.

32. Hammitt LL, Campbell JC, Borys D, et al. Efficacy, safety and immunogenicity of a pneumococcal protein-based vaccine co-administered with 13-valent pneumococcal conjugate vaccine against acute otitis media in young children: a phase IIb randomized study. Vaccine 2019; 37:7482–7492.
Acute bacterial meningitis

Wall et al.

33. Converse TR, Assoni L, Andre GO, et al. The long search for a serotype independent pneumococcal vaccine. Expert Rev Vaccines 2020; 19:59–70.

34. Schumann B, Reppe K, Kaplanov P, et al. Development of an efficacious, semisynthetic glycolipid conjugate vaccine candidate against Streptococcus pneumoniae serotype 1. ACS Cent Sci 2018; 4:357–361.

35. Ramos-Sevillano E, Ercoli G, Felgner P, et al. Preclinical development of virulence attenuated Streptococcus pneumoniae strains able to enhance protective immunity against pneumococcal infection. Am J Respir Crit Care Med. 2020. doi: 10.1164/rcrm.2020-14161E. Online ahead of print. New data suggesting attenuated pneumococcal whole cell vaccines enhance PCV effects.

36. Bai X, Borov R, Bukovski S, et al. Prevention and control of meningococcal disease: updates from the Global Meningococcal Initiative in Eastern Europe. J Infect 2019; 78:529–541.

37. Li J, Shao Z, Liu G, et al. ST-17 clone. Microbes Infect 2006; 8:1714–1722.

38. Iovino F, Engelen-Lee JY, Brouwer M, et al. Free sialic acid acts as a signal that impacts the immune response to meningococcal serogroup C disease: recent advances. Infect Drug Resist 2020; 13:1263–1272.

39. Wright OM, Venturini C, Pojar S, et al. Microinvasion by Streptococcus pneumoniae induces epithelial innate immunity during colonisation at the human mucosal surface. Nat Commun 2019; 10:3060. doi: 10.1038/s41467-019-11005-3. First data showing S. pneumoniae subverting the mucosal epithelium and the associated innate immune response.

40. Tuomanen E. Perspective of a pediatrician: shared pathogenesis of the three most successful pathogens of children. Front Cell Infect Microbiol 2020; 10:585791. doi: 10.3389/ficme.2020.585791.

41. Kremers PH, lees JA, Koomans MM, et al. Benzoalokonium tolerance genes and outcome in Listeria monocytogenes meningitis. Clin Microbiol Infect 2017; 23:265.e1–265.e7.

42. van Kassel MN, van Haeringen KJ, Brouwer MC, et al. The emergence and genomic diversification of a virulent serogroup W:ST-2881(CC175) Neisseria meningitidis clone in the African meningitis belt. Microb Genom 2017; 3:e000120. doi: 10.1099/ mgen.0.000120.

43. Russell NJ, Seale AC, O’Driscoll M, et al. Neuraminidase and its role in nascent human infection of Streptococcus pneumoniae. Clin Microbiol Infect 2020; 26:1257.e1–1257.e7. Epidemiology of influenza and meningococcal meningitis in parallel showing peaks of influenza are followed by outbreaks of meningococcal meningitis.

44. Berardi A, Cassetti T, Creti R, et al. Olfactory ensheathing cell (OEC) behaviour in experimental meningitis models. J Clin Investig 2009; 119:1638–1648.

45. Rivino F, Engeler-Lee JY, Brouwer M, et al. pIlgR and PECA1 bind to pneumococcal adhesins RrgA and PspC mediating bacterial brain invasion. Exp Med 2017; 214:1619–1630.

46. Madoz R, Campos FS, Carvalho LA, et al. Olfactory nerve cell microvascular endothelial cells as putative host cells for Streptococcus pneumoniae: evidence of bacterial invasion via mannose receptor-mediated endocytosis. Neurosci Res 2011; 69:308–313.

47. Munek R, Biles DE. New strategy is needed to prevent pneumococcal meningitis. Pediatr Infect Dis J 2020; 39:298–304.

48. Madoz-Ramos H, Campos FS, Carvalho LA, et al. Olfactory nerve cell microvascular endothelial cells as putative host cells for Streptococcus pneumoniae: evidence of bacterial invasion via mannose receptor-mediated endocytosis. Neurosci Res 2011; 69:308–313.

49. Madoz-Ramos H, Ruiz-Mendoza S, Mariante RM, et al. Streptococcus pneumoniae resist intracellular killing by inflammatory engulfing cells but not by microglia. Scientific Rep 2016; 6:36813. doi: 10.1038/srep36813.

50. Biles DE, Novak L, Hotomi M, et al. Nasal colonization with Streptococcus pneumoniae includes subpopulations of surface and invasive pneumococci. Infect Immun 2005; 73:6945–6951.

51. Hatcher BL, Hale JY, Biles DE. Free sialic acid acts as a signal that promotes Streptococcus pneumoniae invasion of nasal tissue and non-hematogenous invasion of the central nervous system. Infect Immun 2016; 84:2607–2615.

52. Wall EC, Gritzfeld JF, Scarborough M, et al. Genomic pneumococcal load and CSF cytokines are not related to outcome in Malawian adults with meningitis. J Infect 2014; 69:440–448.

53. Kanova E, Tkacova Z, Bhide K, et al. Transcriptome analysis of human brain microvascular endothelial cells response to Neisseria meningitidis and its antigen MaA using RNA-seq. Scientific Rep 2019; 9:18763. doi: 10.1038/s41598-019-55409-y.

54. Too LK, Ya B, Bater AG, et al. Double deficiency of toll-like receptors 2 and 4 alters long-term neurological sequelae in mice cured of pneumococcal meningitis. Scientific Rep 2019; 9:16189. doi: 10.1038/s41598-019-25212-7.

55. Borkowski J, Li L, Steinmann U, et al. Neisseria meningitidis elicits a proinflammatory response involving Ifnar/Ifnbeta in a human blood-cerebrospinal fluid barrier model. J Neuroinflamm 2014; 11:163. doi: 10.1186/s12974-014-0169-x.
CNS inflammatory disorders: infectious diseases

82. van Wel G, Sanders MS, Ouburg S, et al. Polymorphisms in Toll-like receptors 2, 4, and 9 are highly associated with hearing loss in survivors of bacterial meningitis. PLoS One 2012; 7:e5837. doi: 10.1371/journal.pone.005837.

83. Mohanty T, Fisher J, Bakoci A, et al. Neutrophil extracellular traps in the central nervous system hinder bacterial clearance during pneumococcal meningitis. Nat Commun 2019; 10:1967. doi: 10.1038/s41467-019-09040-0.

Data on NETs from human CSF extrapolated to a murine model to show damaging effects of NETs within the CNS, and efficacy of DNase in improving murine survival.

84. Jayaraman K, Sneuro M, Richardson RM, Rajapagol S. How do chemo-kines navigate neutrophils to the target site: dissecting the structural mechanisms and signaling pathways. Cell Signal 2018; 54:69–80.

85. Rupp S, Chandiragand D, Mitchell TJ, et al. Pneumolysin and the bacterial capsule of Streptococcus pneumoniae cooperatively inhibit tachy- and motility of microglia. J Neuroinflamm 2011; 16:105. doi: 10.1186/s12974-019-1491-7.

86. Wall EC, Gordon SB, Hassan S, et al. Persistence of pneumolysin in the cerebrospinal fluid of patients with pneumococcal meningitis is associated with mortality. Clin Infect Dis 2012; 54:701–705.

87. Girdharan VV, Generoso JS, Colodell A, et al. Receptor for advanced glycation end products (RAGE) mediates cognate immunological tolerance induced by pneumococcal meningitis. Neurotherapeutics 2020. doi: 10.1007/s13311-020-00917-3.

88. Chen P, Li NN, Wong BW, et al. Uprolignation of CBP by PLY can cause permeability of blood-brain barrier to increase meningitis. J Biochem Mol Toxicol 2018; 32:e2393. doi: 10.1002/jbt.22333.

89. Wall EC, Gordon SB, Hassan S, et al. Persistence of pneumolysin in the cerebrospinal fluid of patients with pneumococcal meningitis is associated with mortality. Clin Infect Dis 2012; 54:701–705.

101. Li Y, Metcalf BJ, Chochua S, et al. Genome-wide association analyses of invasive pneumococcal isolates identify a missense bacterial mutation associated with meningitis. Nat Commun 2019; 10:178. doi: 10.1038/s41467-018-07997-y.

102. Kremer PHC, Lees JA, Fenwerta B, et al. Genetic variation in Neisseria meningitidis does not influence disease severity in meningococcal meningitis. Front Med (Lausanne) 2020; 7:94769. doi: 10.3389/fmed.2020.00974.

103. Minhas V, Aplinro R, McAllister LJ, et al. In vivo dual RNA-seq reveals that neutrophil recruitment underlies differential tissue tropism of Streptococcus pneumoniae. Commun Biol 2020; 3:293. doi: 10.1038/s42003-020-1018-x.

104. Key study showing differential tissue tropism and mediation of neutrophil recruitment by S. pneumoniae.

105. Minhas V, Harvey C, McAllister LJ, et al. Capacity to utilize raffinose dictates pneumococcal disease phenotype. mBio 2019; 10: doi: 10.1128/mBio.02956-18.

106. Aplinro R, Slager J, Holzap PPP, Veening JW. Time-resolved dual RNA-seq reveals extensive rewiring of lung epithelial and pneumococcal transcriptomes during early infection. Genome Biol 2016; 17:198. doi: 10.1186/s13059-016-1054-5.

107. D’Mello A, Riegler AN, Martise E, et al. In vivo atlas of host-pathogen transcriptomes during Streptococcus pneumoniae colonization and disease. PNAS 2020; 117:33507–33518.

108. Murine and bacterial transcriptomes at different disease sites.

109. Schmidt F, Kakar N, Meyer TC, et al. In vivo proteomics identifies the competence regulon and AI2 oligopeptide transporter as pathogenic factors for meningitis. PLoS Pathog 2019; 15:1007987. doi: 10.1371/journal.ppat.1007987.

110. Azad AK, Chakrabarti S, Xu Z, et al. Coiled-coil domain containing 3 (CCDC3) represses tumor necrosis factor-alpha/nuclear factor kappaB-induced endothelial inflammation. Cell Signal 2014; 26:2793–2800.

111. van Zeggeren IE, Blijlma MW, Tanck MW, et al. Systematic review and meta-analysis for diagnostic prediction models in patients suspected of meningitis. J Infect 2020; 80:143–151.

112. Wall EC, Mukaka M, Scarborough M, et al. Prediction of outcome from adult bacterial meningitis in a high-HIV-seroprevalence, resource-poor setting using the Malawi Adult Meningitis Score (MAMS). Clin Infect Dis 2017; 64:413–419.

113. McGill F, Griffiths MJ, Bonnett LJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. Lancet Infect Dis 2018; 18:992–1003.

114. Haaburn R, Abrams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001; 345:1727–1733.

115. Michael B, Menezes BF, Cunliffe J, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. Emerg Med J 2010; 27:433–438.

116. Vilimaker M, Sijikun J, Akesson S, Naucier P. Lumbar puncture performed promptly or after neuroimaging in acute bacterial meningitis in adults: a prospective national cohort study evaluating different guidelines. Clin Infect Dis 2018; 66:321–328.

117. Salazar L, Hasbun R. Cranial imaging before lumbar puncture in adults with suspected meningitis: the American Academy of Neurology and Infectious Diseases Society of America Guidelines. Clin Infect Dis 2017; 64:1657–1662.

118. Costerus JM, Brouwer MC, Sprengers MES, et al. Cranial computed tomography, lumbar puncture, and clinical deterioration in bacterial meningitis: a nationwide cohort study. Clin Infect Dis 2018; 67:920–926.

119. McGill F, Haydeman RS, Menezes BF, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect 2016; 72:405–458.

120. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016; 22(Suppl 3):S77–S82.

121. Tunley AR, Hasbun R, Bhimpat A, et al. 2017 Infectious Diseases Society of America’s clinical practice guidelines for healthcare-associated ventilitis and meningitis. Clin Infect Dis 2017; 64:a48–655.

122. Wu HM, Cordeiro SM, Harcourt BH, et al. Accuracy of real-time PCR, Gram stain and culture for Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae meningitis diagnosis. BMC Infect Dis 2015; 13:26. doi: 10.1186/1471-2334-13-26.

123. Houhun CF, Buhurua T, Broujer A. Advances in molecular diagnostic testing for central nervous system infections. Curr Opin Infect Dis 2019; 22:244–250.

124. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med 2019; 380:2327–2340.

125. First report of the clinical utility of NGS for the diagnosis of culture negative meningitis.

126. Costerus JM, Brouwer MC, Blijlma MW, et al. Impact of an evidence-based guideline on the management of community-acquired bacterial meningitis: a prospective cohort study. Clin Microbiol Infect 2016; 22:928–933.

127. Panagiotou S, Chaguza C, Yahya R, et al. Polymorphism in Toll-like receptors 2, 4, and 9 are highly associated with hearing loss in survivors of bacterial meningitis. PLoS One 2012; 7:e5837. doi: 10.1371/journal.pone.005837.

128. Mogensen TH, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016; 22(Suppl 3):S77–S82.

129. Tunley AR, Hasbun R, Bhimpat A, et al. 2017 Infectious Diseases Society of America’s clinical practice guidelines for healthcare-associated ventilitis and meningitis. Clin Infect Dis 2017; 64:a48–655.

130. Wu HM, Cordeiro SM, Harcourt BH, et al. Accuracy of real-time PCR, Gram stain and culture for Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae meningitis diagnosis. BMC Infect Dis 2015; 13:26. doi: 10.1186/1471-2334-13-26.

131. Houhun CF, Buhurua T, Broujer A. Advances in molecular diagnostic testing for central nervous system infections. Curr Opin Infect Dis 2019; 22:244–250.

132. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med 2019; 380:2327–2340.

133. First report of the clinical utility of NGS for the diagnosis of culture negative meningitis.
Acute bacterial meningitis Wall et al.

127. Wall EC, Mukaka M, Denis B Goal directed therapy for suspected acute bacterial meningitis in adults and adolescents in sub-Saharan Africa. PLoS One 2017; 12:e0186687. doi: 10.1371/journal.pone.0186687.

128. Nhantumbo AA, Gudo ES, Caierao J, Munguambe AM, et al. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae in children with acute bacterial meningitis in Mozambique: implications for a national immunization strategy. BMC Microbiol 2016; 16:134. doi: 10.1186/s12866-016-0747-y.

129. Comick JE, Everett DB, Broughton C, et al. Invasive Streptococcus pneumoniae in children, Malawi, 2004–2006. Emerging Infect Dis 2011; 17:1107–1109.

130. Wen S, Feng D, Chen D, et al. Molecular epidemiology and evolution of Haemophilus influenzae. Infect Genet Evol 2020; 80:104205. doi: 10.1016/j.meegid.2020.104205.

131. Tenforde MW, Mokomane M, Leeme TB, et al. Mortality in adult patients with culture-positive and culture-negative meningitis in the Botswana national meningitis survey: a prevalent cohort study. Lancet Infect Dis 2019; 19:740–749.

Data highlighting the excessive mortality from bacterial meningitis in Africa.

132. Kloek AT, Brouwer MC, Schmand B, et al. Long-term neurologic and cognitive outcome and quality of life in adults after pneumococcal meningitis. Clin Microbiol Infect 2020; 26:1361–1367.

133. Klein M, Koedel U, Pfefferkorn T, et al. Arterial cerebrovascular complications in 94 adults with acute bacterial meningitis. Crit Care 2011; 15:R281. doi: 10.1186/cc10565.

134. Klein M, Koedel U, Kastenbauer S, et al. Delayed cerebral thrombosis after initial good recovery from pneumococcal meningitis: past as prologue: delayed stroke as a parainfectious process of bacterial meningitis? Neurology 2010; 75:193author reply 193–4.

135. Engelen-Lee JY, Brouwer MC, Aronica E, van de Beek D. Delayed cerebral thrombosis complicating pneumococcal meningitis: an autopsy study. Ann Intensive Care 2018; 8:20. doi: 10.1186/s13613-018-0568-8.

136. Lucas MJ, Brouwer MC, van de Beek D. Delayed cerebral thrombosis in bacterial meningitis: a prospective cohort study. Intensive Care Med 2013; 39:866–871.

137. van de Beek D, Farrar JJ, de Gans J, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. Lancet Neurol 2010; 9:254–263.

138. Nguyen TH, Tran TH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 2007; 357:2431–2440.

139. Scarborough M, Gordon SB, Whitty CJ, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007; 357:2441–2450.

140. Ajdukiewicz RM, Cartwright KE, Scarborough M, et al. Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomised controlled trial. Lancet Infect Dis 2011; 11:293–300.

141. Mourvillier B, Tubach F, van de Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomized clinical trial. JAMA 2013; 310:2174–2183.

142. Ribes S, Taberner F, Domenech A, et al. Evaluation of ceftriaxone, vancomycin and rifampicin alone and combined in an experimental model of meningitis caused by highly cephalosporin-resistant Streptococcus pneumoniae ATCC 51918. J Antimicrob Chemother 2005; 56:979–982.

143. Wald-Dickler N, Hoftom P, Spellberg B. Busting the myth of ‘static vs cidal’: a systemic literature review. Clin Infect Dis 2018; 66:1470–1474.

144. Grandgirard D, Schurch C, Cottagnoud P, Leib SL. Prevention of brain injury by the nonbacteriolytic antibiotic daptomycin in experimental pneumococcal meningitis. Antimicrob Agents Chemother 2007; 51:2173–2178.

145. Kasamontaib L, Valls Seron M, et al. Adjuvant treatment with dexamethasone plus anti-C5 antibodies improves outcome of experimental pneumococcal meningitis: a randomized controlled trial. J Neuroinflamm 2015; 12:149. doi: 10.1186/s12974-015-0372-y.

146. Muri L, Le ND, Zemp J, et al. Metformin mediates neuroprotection and attenuates hearing loss in experimental pneumococcal meningitis. J Neuroinflamm 2019; 16:156. doi: 10.1186/s12974-019-1549-6.

147. Mai NT, Dobbs N, Phu NH, et al. A randomised double blind placebo controlled phase 2 trial of adjunctive aspirin for tuberculous meningitis in HIV-uninfected adults. eLife 2018; 7. doi: 10.7554/eLife.33478.

148. Liechti FD, Grandgirard D, Leppert D, Leib SL. Matrix metalloproteinase inhibition lowers mortality and brain injury in experimental pneumococcal meningitis. Infect Immun 2014; 82:1710–1718.

149. Morton B, Mitzi E, Pennington SH, et al. Augmented passive immunotherapy with P4 peptide improves phagocyte activity in severe sepsis. Shock 2016; 46:635–641.

150. Jim KK, Engelen-Lee J, van der Sar AM, et al. Infection of zebrafish embryos with live fluorescent Streptococcus pneumoniae as a real-time pneumococcal meningitis model. J Neuroinflamm 2016; 13:188. doi: 10.1186/s12974-016-0655-y.