REVIEW

From the microbiome to the central nervous system, an update on the epidemiology and pathogenesis of bacterial meningitis in childhood [version 1; referees: 3 approved]

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v1 **First published:** 27 Jan 2017, **6**(F1000 Faculty Rev):86 (doi: 10.12688/f1000research.8533.1)

Latest published: 27 Jan 2017, **6**(F1000 Faculty Rev):86 (doi: 10.12688/f1000research.8533.1)

Abstract

In the past century, advances in antibiotics and vaccination have dramatically altered the incidence and clinical outcomes of bacterial meningitis. We review the shifting epidemiology of meningitis in children, including after the implementation of vaccines that target common meningitic pathogens and the introduction of intrapartum antibiotic prophylaxis offered to mothers colonized with *Streptococcus agalactiae*. We also discuss what is currently known about the pathogenesis of meningitis. Recent studies of the human microbiome have illustrated dynamic relationships of bacterial and viral populations with the host, which may potentiate the risk of bacterial meningitis.

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How to cite this article: Janowski AB and Newland JG. **From the microbiome to the central nervous system, an update on the epidemiology and pathogenesis of bacterial meningitis in childhood [version 1; referees: 3 approved]** *F1000Research* 2017, **6**(F1000 Faculty Rev):86 (doi: 10.12688/f1000research.8533.1)

Grant information: The author(s) declared that no grants were involved in supporting this work.

Competing interests: The authors declare that they have no competing interests.

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Introduction

At the turn of the 20th century, bacterial meningitis was an almost universally fatal disease. Two important medical advances—antibiotics and vaccination—have dramatically decreased the incidence and the case fatality rate of bacterial meningitis, particularly within pediatric populations. Some of the pathogens that caused meningitis 20 years ago are now more likely to be encountered by medical trainees in reviewing textbooks than in clinical practice. With these shifting dynamics, a greater understanding of the current epidemiology of community-acquired meningitis is needed. In addition, several pathways involved in the pathogenesis of bacterial meningitis have been elucidated. We review some of these models and provide an update on the role of the microbiome in the development of meningitis.

Overview of the epidemiology of bacterial meningitis in childhood

Traditional descriptions of bacterial meningitis in childhood have stratified causative pathogens on the basis of age, as there is a stark contrast in the bacterial pathogens that cause meningitis in newborns compared with older children. Meningitis in children older than 60 days, called "pediatric bacterial meningitis" in this review, is often caused by encapsulated bacteria that colonize the nasopharynx and other body sites. Meningitis in children younger than 60 days, called "young infant bacterial meningitis" in this review, is further stratified by gestational age and timing of onset of infection[1]. In general, infections that occur within the first 7 days of life of a term neonate are described as early onset disease, whereas infections occurring from 7 to 60 days after birth are described as late-onset disease[1]. Early onset disease is caused predominantly by bacteria transmitted at the time of parturition, whereas late-onset disease is caused by members of the microbiome transmitted at birth or through exposures after birth, such as maternal contact or method of feeding[1–5]. Despite the distinctions in pathogens between the age cohorts, pathogens of pediatric bacterial meningitis can also cause disease in young infants and vice versa.

Pediatric bacterial meningitis

For over 30 years, the Centers for Disease Control and Prevention (CDC) in the US has published surveillance data of bacterial meningitis. In 1995, the CDC established the Active Bacterial Core Surveillance, an active monitoring system for invasive pathogens, and since then has made annual reports available to the public (http://www.cdc.gov/abcs/reports-findings/surv-reports.html). The epidemiology of meningitis in the US has profoundly changed over the past several decades. In 1978–1981, *Haemophilus influenzae* was the most frequent cause of meningitis (48.3% of cases), followed by *Neisseria meningitidis* (19.6%) and *Streptococcus pneumoniae* (13.3%)[6]. By 2014, in children under age 5 in the US, *S. pneumoniae* was the most frequently identified pathogen whereas *H. influenzae* was rarely detected[7].

Although *S. pneumoniae* is the most frequent etiology of bacterial meningitis in the US, the incidence of pneumococcal meningitis has dramatically decreased over the past two decades because of the implementation of pneumococcal serotype vaccines (Figure 1a)[8]. In 2000, a seven-valent pneumococcal vaccine (PCV7) targeting a subset of serotypes associated with invasive disease was licensed in the US[8]. After the introduction of PCV7, the rate of invasive disease caused by PCV7 serotypes fell from 80 per 100,000 population in 2000 to below one per 100,000 population in 2007[9]. Meningitis caused by PCV7 serotypes also significantly decreased, from 8.2 cases per 100,000 in 1998–1999 to 0.59 cases per 100,000 in 2004–2005[10]. Substantial reductions in invasive pneumococcal infections were also observed in other countries after implementation of the PCV7 vaccine[11,12]. However, surveillance data identified a rise in the incidence of meningitis caused by serotypes not included in the vaccine, known as serotype replacement[13], prompting the development of a 13-valent pneumococcal vaccine (PCV13) licensed in the US in 2010. Since the implementation of PCV13 in several countries, continued decreases in invasive *S. pneumoniae* diseases have been observed (Figure 1a)[14–20]. However, there are conflicting data as to whether the introduction of PCV13 has decreased the rate of *S. pneumoniae* meningitis[20–22].

The dramatic reduction in the incidence of *H. influenzae* meningitis demonstrates the tremendous success of the serotype B vaccine[23]. *H. influenzae* type B is a highly virulent strain that caused the majority of *H. influenzae* meningitis cases[23,24]. In 1978–1981, the peak incidence of *H. influenzae* meningitis was in infants 9 to 11 months of age, and the attack rate was 70 cases

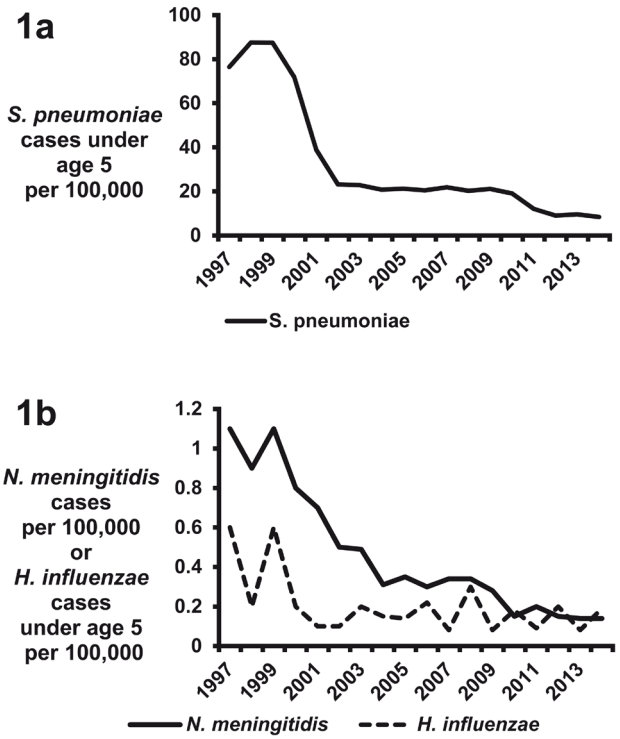

Figure 1. Rates of (**a**) invasive disease for *Streptococcus pneumoniae* in children under the age of 5 and (**b**) invasive disease caused by *Haemophilus influenzae* in children under the age of 5 and by *Neisseria meningitides* in all ages. All data are from accumulated Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance reports 1997–2014 (http://www.cdc.gov/abcs/reports-findings/surv-reports.html).

of meningitis per 100,000 population per year[6]. In the 1980s, several *H. influenzae* type B vaccines were in development; among them were an unconjugated polysaccharide formulation licensed in the US in 1985 and the conjugate vaccine licensed in the US in 1987. Implementation of the vaccines caused a rapid decline in *H. influenzae* disease; by 2014, the CDC identified only 40 invasive cases of *H. influenzae* type B infection, representing an invasive disease rate of 0.19 per 100,000 US children under the age of 5 (Figure 1b)[25–27]. Similar analyses in other countries have also demonstrated a significant reduction of *H. influenzae* meningitis after implementation of the type B vaccine[11,12,28].

For *N. meningitidis*, 13 serogroups are currently known and only six serogroups are recognized to cause meningitis (A, B, C, W-135, X, and Y)[29]. During 1978–1981 in the US, the highest rate of *N. meningitidis*-associated meningitis was in children aged 3 to 5 months, with over 10 cases per 100,000 population per year[6]. Over the next 25 years, the incidence of meningitis caused by *N. meningitidis* decreased in the US and this was hypothesized to be due to a combination of environmental, organism, and host factors (Figure 1b)[30]. In 2005, the meningococcal conjugate quadrivalent vaccine (MenACWY) targeting serogroups A, C, Y, and W-135 was licensed for use in adolescents in the US. Further reductions in disease have been observed after implementation of the vaccine; in 2014, meningococcemia occurred in 0.14 cases per 100,000 persons in the US, representing a total of 443 invasive cases[27]. Infants under a year of age have the highest incidence of meningitis from *N. meningitidis*; an estimated 2.74 cases of meningitis per 100,000 occurred in the US from 2006 to 2012[31]. From that same study, serogroup B caused 64% of cases of meningitis, serogroup Y caused 16%, and serogroup C caused 12%[31]. Similar reductions in *N. meningitidis*-associated diseases have been observed in other countries after the implementation of vaccination strategies[12,32,33]. *N. meningitidis* is a well-known cause of meningitis epidemics in the sub-Saharan region of Africa, where attack rates are as high as 800 cases per 100,000 population[34,35]. Serogroup A accounts for 80–85% of all outbreak cases, and many global efforts in distributing vaccines to epidemic regions of Africa have significantly reduced the incidence of meningitis[35,36].

Young infant bacterial meningitis

In older studies, *Streptococcus agalactiae* (Group B Streptococcus, or GBS) was the most frequently identified pathogen from cases of young infant bacterial meningitis, followed in incidence by other organisms, including *Escherichia coli* and *Listeria monocytogenes*[37–42]. In a 2014 study from the UK and Ireland, GBS remained the most common cause of meningitis despite interventions to reduce disease caused by this organism[43]. This result contrasts with a 2014 study of young infants in California, where *E. coli* was the most frequently identified pathogen in meningitis[44]. Other recent studies have described the importance of enteric Gram-negative organisms causing meningitis in this age group, while the incidence of meningitis caused by *L. monocytogenes* has decreased[44–46].

The primary reason behind the shift in the epidemiology in the US has been the implementation of intrapartum antibiotic prophylaxis against GBS[39,47,48]. The CDC, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists published unified prophylaxis guidelines in 1996, screening guidelines in 2002, and revised guidelines in 2010[49–55]. Pregnant mothers are screened for rectovaginal colonization at 35 to 37 weeks' gestation for GBS, and colonized mothers are provided with intrapartum antibiotic prophylaxis[52–54]. Additionally, intrapartum antibiotics are indicated for mothers if they have a previous infant with invasive GBS disease, history of GBS bacteriuria, or unknown GBS status with at least one of the following: delivery at less than 37 weeks' gestation, amniotic membrane rupture of at least 18 hours, fever, or an intrapartum nucleic acid amplification test (NAAT) positive for GBS[55]. Efficacy of reducing transmission is enhanced if a beta-lactam or cephalosporin antibiotic is given at least 4 hours prior to delivery[56,57]. This intervention has dramatically reduced the rates of early onset sepsis from GBS, including meningitis (Figure 2a)[48]. However, intrapartum prophylaxis has not reduced the rate of late-onset GBS invasive disease (Figure 2a)[48,58,59]. Multiple factors likely contribute to the unchanged incidence of GBS late-onset disease, as intrapartum antibiotics reduce but do not abrogate GBS colonization, and transmission of GBS after birth may also occur through maternal, nosocomial, or environmental contacts[3,59].

The overall incidence of meningitis and sepsis from *E. coli* has remained relatively stable in term infants since the implementation of GBS prophylaxis guidelines in the US and France[60–64]. However,

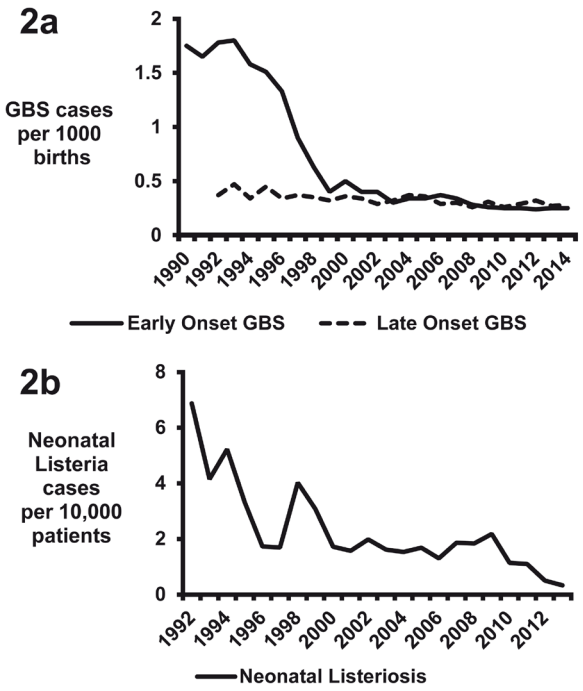

Figure 2. Rates of invasive young infant infections in the United States. (**a**) Early onset Group B Streptococcus (GBS) disease data for 1990 to 1998 are from 47 and for 1999 to 2014 are from accumulated Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance reports. Late-onset GBS disease data for 1992–2005 are from 59 and for 2006–2014 are from accumulated CDC Active Bacterial Core surveillance reports. (**b**) Listeria data are from 82.

trends of increasing frequency of disease in select subgroups have been described, including an increase of *E. coli* early onset sepsis in preterm or very-low-birth-weight neonates[1,64–66]. The incidence of late-onset disease from *E. coli* has also increased in term or preterm infants[1,64–66]. *E. coli* isolated from cases of meningitis is frequently resistant to ampicillin[45,60], but an increase in ampicillin-resistant *E. coli* has been observed only in low-birth-weight or premature infants[60,67–69]. Recent analyses of the infant gastrointestinal microbiome have identified the presence of many antibiotic-resistance genes, but it is not known why the frequency of resistant *E. coli* invasive disease has not increased in all young infants during the period of intrapartum prophylaxis[70–74].

Previously in the US, *L. monocytogenes* was a common cause of neonatal meningitis, but in 2014 only 13 cases of meningitis and 37 cases of bacteremia were reported in neonates[75]. Based on the birth data for the US in 2014 (3,988,076 total births), the 50 cases of neonatal listeriosis would translate to a rate of 1.25 invasive cases per 100,000 births. This is in stark contrast to 17.4 invasive cases per 100,000 births in 1989, which decreased to 8.6 cases per 100,000 births by 1993[76]. Increased safety in food product handling was the major driving force in the reduction of cases in the US during the 1980s and 1990s[77–79]. By 2004–2009, seven cases per 100,000 births on average were complicated by *L. monocytogenes* infection, according to estimates calculated by using data from Silk *et al.*[80] and the US birth rate[81]. The GBS intrapartum prophylaxis recommendations may have contributed to the reduction of listeriosis, as the primary antibiotics used for prophylaxis—penicillin G and ampicillin—have excellent activity against *L. monocytogenes*[82]. Supporting this hypothesis are reduced rates of invasive disease in infants under 30 days of life identified from the Pediatric Health Information System, a database that uses pediatric discharge data from 45 tertiary pediatric hospitals in the US[82]. A total of 6.87 listeria cases per 10,000 patients occurred in 1992 compared with 0.33 cases per 10,000 patients in 2013, and this correlated with the reduction in GBS invasive diseases (Figure 2b)[82].

Pathogenesis of meningitis

The pathogenesis of bacterial meningitis is often characterized by four primary processes: (1) colonization of the epithelial barrier, (2) entrance into the circulatory system, (3) breeching of the blood-brain barrier (BBB), and (4) central nervous system (CNS) inflammation and injury (Figure 3)[83–86].

Epithelial surfaces in humans are the interface in which complex interactions develop among the host, environment, and diverse populations of organisms. *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, and many other bacterial organisms colonize the nasopharyngeal tract, being freely exchanged by aerosolization and contact with secretions[87,88]. Although these organisms collectively inhabit the nasopharynx, this colonization is not necessarily a peaceful co-inhabitation between organisms; rather it is an evolving balance among mutualism, competition, and outright antagonism. *S. pneumoniae* can produce hydrogen peroxide that causes a rapid decrease in the growth of *H. influenzae*[89]. Likewise, *H. influenzae* type B can induce an immune response that selectively targets *S. pneumoniae* while leaving *H. influenzae* colonies unscathed[90,91]. Vaccination efforts have also altered the composition of the nasopharyngeal microbiome and have altered the epidemiology of acute otitis media[92,93]. Ultimately, there are many interbacterial interactions in the nasopharynx, and further investigation may reveal compositions of the microbiome that modify the risk of meningitis[92,94,95].

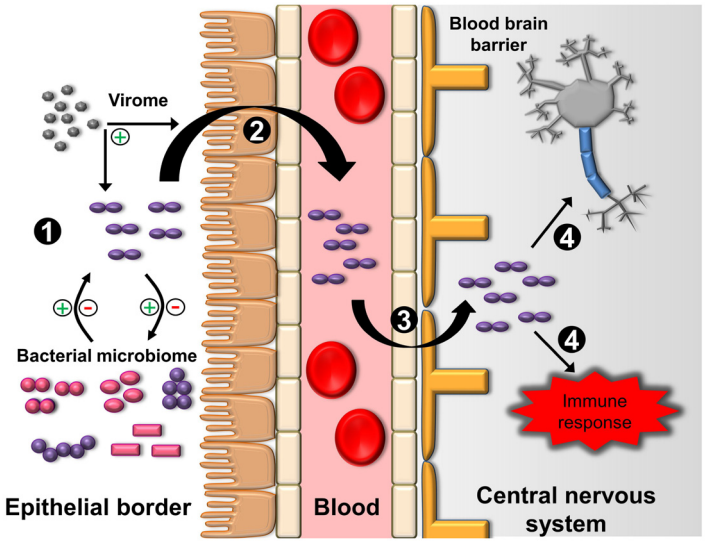

Figure 3. Four generalized steps are involved in the pathogenesis of bacterial meningitis. (**1**) Bacterial colonization of the epithelial border. Colonization is affected by the host and other members of the microbiome, including bacteria and viruses (virome). Bacteria may have synergistic or antagonistic effects on colonization, while viruses may enhance colonization. (**2**) Bacterial invasion of the epithelial surface into the bloodstream. This process can be enhanced by viruses. (**3**) Bacterial breeching of the blood-brain barrier. Various pathways have been described in the penetration of the blood-brain barrier, including transcellular, paracellular, and "Trojan horse" mechanisms of entry. (**4**) Bacterial replication in the central nervous system. The release of bacterial products causes direct toxicity to neurons and stimulation of the immune response, which contributes to additional neurotoxicity.

Interactions with the host are not limited to the bacterial domain, as co-inhabitation of specific viruses with bacteria led to synergistic relationships[88]. Viruses can contribute to bacterial adherence to epithelial surfaces through viral factors and upregulation of host adhesion proteins[88]. Viruses also can contribute to the bacterial invasion of the epithelial surfaces by causing disruption of the epithelial barrier and by impairing the immune response[88,96–98]. Associations between viral infection and meningitis have been observed, and these associations may partially explain outbreaks or seasonality of meningitis[99–103].

Most of the bacterial pathogens of young infant and pediatric meningitis contain a polysaccharide capsule that contributes to invasion of the epithelial surface and survival in the bloodstream[48,84,104–109]. The capsule is an important virulence factor that confers added protection from phagocytosis, complement pathways, and penetration of the epithelium and BBB[48,84,85,110–112]. Children with antibody deficiencies, defects of the complement pathway, or asplenia are at particular risk from invasive disease of these pathogens because of their diminished ability to target and clear encapsulated pathogens from the bloodstream[113].

Bacterial pathogens most often reach the BBB via the bloodstream. A threshold of bacteremia contributes to the breeching of the BBB, as a higher quantity of bacteria in the bloodstream is associated with increased risk of developing meningitis[104,114–117]. Various mechanisms of bacterial factors have been established in the penetration of the BBB. The capsule can aid in bacterial transcellular crossing of the BBB, along with other attachment proteins[83–85,104,118]. Other mechanisms of crossing the BBB, including paracellular pathways or the "Trojan horse" mechanism of infected phagocytes, have been identified[83–85,104]. Meningitis can also occur through direct compromise of the BBB, and mechanisms include penetrating injuries, congenital defects, adjacent infections with erosion into the CNS, or neurosurgical procedures[119–125].

Upon entry of bacterial pathogens into the CNS, they rapidly divide, as the CNS is devoid of complement, antibodies, and opsonic proteins[85,86]. The immune response is activated by Toll-like receptors and Nod-like receptors recognizing pathogen-associated molecular patterns[126,127]. These signaling pathways lead to the production of proinflammatory cytokines and mobilization of the immune response, leading to pleocytosis of white blood cells[83–86,126]. Bacterial cell wall material, enzymes, and toxins cause direct injury to neurons and indirect damage by increasing vascular permeability that causes edema and further injury[83–86]. Neuronal injury is also caused by toxic molecules released by the immune response, including reactive oxygen species, nitrous oxide, and peroxynitrite[84–86]. The release of proteases and excitatory amino acids by the immune response also contributes to neurotoxicity[84–86].

Special considerations of young infant meningitis

Inoculation of bacteria into mucosal surfaces occurs prior to and during parturition with subsequent bacterial invasion causing early onset sepsis[48]. Late-onset sepsis is associated with a period of asymptomatic bacterial colonization and subsequent invasion[3–5]. Two sites of colonization likely contribute to cases of late-onset meningitis. The gastrointestinal tract serves as a frequent site of colonization for *E. coli*, GBS, and *L. monocytogenes*, and all of these pathogens have essential factors that allow for epithelial adherence and invasion[48,85,128]. GBS is readily transmitted from mother to neonate; 29–85% (mean rate of approximately 50%) of infants born to a GBS-positive mother become colonized[48]. The second potential site of colonization is the urinary tract, which may harbor asymptomatic bacteriuria[129,130]. Ascending infection can lead to seeding of the kidney, bacteremia, and then meningitis, as around 13.2% of febrile young infants will present with a urinary tract infection, and a smaller subset will have simultaneous evidence of bacteriuria, bacteremia, and meningitis[44,131].

In premature infants, bacteremic events can be preceded by colonization of the gut by the causative pathogen[132]. In a prospective monitoring of stool samples, Carl *et al*. captured seven cases of sepsis in which the causative bacterial pathogen was also identified from the patient's stool sample preceding the episode of bacteremia[132]. It is unclear whether similar events occur in term infants or within other body sites that contribute to invasion of these bacterial organisms. The effects of intrapartum antibiotics on the infant microbiome are also being elucidated, as the gastrointestinal microbiome of infants born to mothers who received intrapartum antibiotics is different from that of infants born to untreated mothers[133–136]. However, the consequences, if any, of these microbial communities for the risk of meningitis are unknown.

Recent analysis of the microbiome has shown dynamic colonization of the neonatal gut, and one potential factor in colonization is the population of bacteriophages[137,138]. In a longitudinal study of healthy twins, the neonatal bacterial microbiome gained bacterial diversity with increased age, and conversely bacteriophage diversity decreased with age[137]. This may suggest an essential relationship between bacteriophages and development of the gut bacterial microbiome, in which the bacteriophage population guides the diversity of the bacterial population. Further data are needed to determine whether the risk of invasive bacterial disease is increased by certain compositions of the microbiome and whether bacteriophage populations potentiate this risk[139].

The relatively immature immune system of the neonate also contributes to the invasive risk of bacterial pathogens[140–142]. Defects in phagocytic cell function, chemotaxis, cytokine production, complement pathways, Toll-like receptor responses, and antibody production are further conducive to invasive disease[140–142]. These defects also include adaptive immunity in response to viral infections, including lymphocyte proliferation and antibody responses[142–144]. Though significant, these immune defects are transient, likely contributing to the decreased incidence of serious bacterial infections with increasing age.

Conclusions

The incidence of bacterial meningitis in children has been dramatically reduced and this is primarily because of immunization and intrapartum prophylaxis strategies. Nonetheless, *E. coli*, GBS,

S. pneumoniae, and *N. meningitidis* remain important pathogens of meningitis. Recent advances in the analysis of the microbiome have expanded the understanding of the pathogenesis of meningitis. These new insights will provide new avenues of research and may stimulate the development of future treatments to prevent and treat meningitis.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

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1. F Simonsen KA, Anderson-Berry AL, Delair SF, *et al.*: **Early-onset neonatal sepsis.** *Clin Microbiol Rev.* 2014; **27**(1): 21–47.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
2. Le Doare K, Kampmann B: **Breast milk and Group B streptococcal infection: vector of transmission or vehicle for protection?** *Vaccine.* 2014; **32**(26): 3128–32.
PubMed Abstract | Publisher Full Text | Free Full Text
3. Berardi A, Cattelani C, Creti R, *et al.*: **Group B streptococcal infections in the newborn infant and the potential value of maternal vaccination.** *Expert Rev Anti Infect Ther.* 2015; **13**(11): 1387–99.
PubMed Abstract | Publisher Full Text
4. Dong Y, Speer CP: **Late-onset neonatal sepsis: recent developments.** *Arch Dis Child Fetal Neonatal Ed.* 2015; **100**(3): F257–63.
PubMed Abstract | Publisher Full Text | Free Full Text
5. Barichello T, Fagundes GD, Generoso JS, *et al.*: **Pathophysiology of neonatal acute bacterial meningitis.** *J Med Microbiol.* 2013; **62**(Pt 12): 1781–9.
PubMed Abstract | Publisher Full Text
6. Schlech WF 3rd, Ward JI, Band JD, *et al.*: **Bacterial meningitis in the United States, 1978 through 1981. The National Bacterial Meningitis Surveillance Study.** *JAMA.* 1985; **253**(12): 1749–54.
PubMed Abstract | Publisher Full Text
7. Centers for Disease Control and Prevention: **Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae*, 2014.** 2014.
Reference Source
8. Nuorti JP, Whitney CG; Centers for Disease Control and Prevention (CDC): **Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR Recomm Rep.* 2010; **59**(RR-11): 1–18.
PubMed Abstract
9. Cox CM, Link-Gelles R: **Chapter 11: Pneumococcal.** In *Manual for the surveillance of vaccine-preventable diseases.* (ed), Dept. of Health and Human Services Centers for Disease Control and Prevention, Atlanta, Ga. 2012.
Reference Source
10. F Hsu HE, Shutt KA, Moore MR, *et al.*: **Effect of pneumococcal conjugate vaccine on pneumococcal meningitis.** *N Engl J Med.* 2009; **360**(3): 244–56.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
11. Brouwer MC, Tunkel AR, van de Beek D: **Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis.** *Clin Microbiol Rev.* 2010; **23**(3): 467–92.
PubMed Abstract | Publisher Full Text | Free Full Text
12. McIntyre PB, O'Brien KL, Greenwood B, *et al.*: **Effect of vaccines on bacterial meningitis worldwide.** *Lancet.* 2012; **380**(9854): 1703–11.
PubMed Abstract | Publisher Full Text
13. Weinberger DM, Malley R, Lipsitch M: **Serotype replacement in disease after pneumococcal vaccination.** *Lancet.* 2011; **378**(9807): 1962–73.
PubMed Abstract | Publisher Full Text | Free Full Text
14. F Moore MR, Link-Gelles R, Schaffner W, *et al.*: **Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance.** *Lancet Infect Dis.* 2015; **15**(3): 301–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
15. F Levy C, Varon E, Picard C, *et al.*: **Trends of pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in France.** *Pediatr Infect Dis J.* 2014; **33**(12): 1216–21.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
16. F Andrews NJ, Waight PA, Burbidge P, *et al.*: **Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study.** *Lancet Infect Dis.* 2014; **14**(9): 839–46.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
17. F Ben-Shimol S, Greenberg D, Givon-Lavi N, *et al.*: **Early impact of sequential introduction of 7-valent and 13-valent pneumococcal conjugate vaccine on IPD in Israeli children <5 years: an active prospective nationwide surveillance.** *Vaccine.* 2014; **32**(27): 3452–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
18. Demczuk WH, Martin I, Griffith A, *et al.*: **Serotype distribution of invasive *Streptococcus pneumoniae* in Canada after the introduction of the 13-valent pneumococcal conjugate vaccine, 2010–2012.** *Can J Microbiol.* 2013; **59**(12): 778–88.
PubMed Abstract | Publisher Full Text
19. F Harboe ZB, Dalby T, Weinberger DM, *et al.*: **Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality.** *Clin Infect Dis.* 2014; **59**(8): 1066–73.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
20. F Guevara M, Ezpeleta C, Gil-Setas A, *et al.*: **Reduced incidence of invasive pneumococcal disease after introduction of the 13-valent conjugate vaccine in Navarre, Spain, 2001–2013.** *Vaccine.* 2014; **32**(22): 2553–62.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
21. F Olarte L, Barson WJ, Barson RM, *et al.*: **Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis in US Children.** *Clin Infect Dis.* 2015; **61**(5): 767–75.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
22. F Cohen R, Biscardi S, Levy C: **The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014.** *Hum Vaccin Immunother.* 2016; **12**(2): 277–84.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
23. F Thigpen MC, Whitney CG, Messonnier NE, *et al.*: **Bacterial meningitis in the United States, 1998–2007.** *N Engl J Med.* 2011; **364**(21): 2016–25.
PubMed Abstract | Publisher Full Text | F1000 Recommendation
24. Pittman M: **Variation And Type Specificity In The Bacterial Species Hemophilus Influenzae.** *J Exp Med.* 1931; **53**(4): 471–92.
PubMed Abstract | Publisher Full Text | Free Full Text
25. Adams D, Fullerton K, Jajosky R, *et al.*: **Summary of Notifiable Infectious Diseases and Conditions - United States, 2013.** *MMWR Morb Mortal Wkly Rep.* 2015; **62**(53): 1–122.
PubMed Abstract | Publisher Full Text
26. Centers for Disease Control and Prevention: **Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Haemophilus influenza* 2014.** 2014.
Reference Source
27. Adams DA, Thomas KR, Jajosky RA, *et al.*: **Summary of Notifiable Infectious Diseases and Conditions - United States, 2014.** *MMWR Morb Mortal Wkly Rep.* 2016; **63**(54): 1–152.
PubMed Abstract | Publisher Full Text
28. Peltola H: **Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates.** *Clin Microbiol Rev.* 2000; **13**(2): 302–17.
PubMed Abstract | Publisher Full Text | Free Full Text
29. Rouphael NG, Stephens DS: ***Neisseria meningitidis*: biology, microbiology, and epidemiology.** *Methods Mol Biol.* 2012; **799**: 1–20.
PubMed Abstract | Publisher Full Text | Free Full Text
30. Cohn AC, MacNeil JR, Harrison LH, *et al.*: **Changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998–2007: implications for prevention of meningococcal disease.** *Clin Infect Dis.* 2010; **50**(2): 184–91.
PubMed Abstract | Publisher Full Text
31. F MacNeil JR, Bennett N, Farley MM, *et al.*: **Epidemiology of infant meningococcal disease in the United States, 2006–2012.** *Pediatrics.* 2015; **135**(2): e305–11.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

32. Sáfadi MA, McIntosh ED: **Epidemiology and prevention of meningococcal disease: a critical appraisal of vaccine policies.** *Expert Rev Vaccines.* 2011; **10**(12): 1717–30.
PubMed Abstract | Publisher Full Text

33. Borrow R, Alarcón P, Carlos J, *et al.*: **The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection.** *Expert Rev Vaccines.* 2016: 1–16.
PubMed Abstract | Publisher Full Text

34. Scarborough M, Thwaites GE: **The diagnosis and management of acute bacterial meningitis in resource-poor settings.** *Lancet Neurol.* 2008; **7**(7): 637–48.
PubMed Abstract | Publisher Full Text

35. F Cohn A, MacNeil J: **The Changing Epidemiology of Meningococcal Disease.** *Infect Dis Clin North Am.* 2015; **29**(4): 667–77.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

36. Collard J, Issaka B, Zaneidou M, *et al.*: **Epidemiological changes in meningococcal meningitis in Niger from 2008 to 2011 and the impact of vaccination.** *BMC Infect Dis.* 2013; **13**: 576.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Gladstone IM, Ehrenkranz RA, Edberg SC, *et al.*: **A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience.** *Pediatr Infect Dis J.* 1990; **9**(11): 819–25.
PubMed Abstract | Publisher Full Text

38. Wiswell TE, Baumgart S, Gannon CM, *et al.*: **No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed?** *Pediatrics.* 1995; **95**(6): 803–6.
PubMed Abstract

39. Camacho-Gonzalez A, Spearman PW, Stoll BJ: **Neonatal infectious diseases: evaluation of neonatal sepsis.** *Pediatr Clin North Am.* 2013; **60**(6): 367–89.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Gaschignard J, Levy C, Romain O, *et al.*: **Neonatal Bacterial Meningitis: 444 Cases in 7 Years.** *Pediatr Infect Dis J.* 2011; **30**(3): 212–7.
PubMed Abstract | Publisher Full Text

41. Chang C, Chang WN, Huang LT, *et al.*: **Bacterial meningitis in infants: the epidemiology, clinical features, and prognostic factors.** *Brain Dev.* 2004; **26**(3): 168–75.
PubMed Abstract | Publisher Full Text

42. Edmond KM, Kortsalioudaki C, Scott S, *et al.*: **Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis.** *Lancet.* 2012; **379**(9815): 547–56.
PubMed Abstract | Publisher Full Text

43. F Okike IO, Johnson AP, Henderson KL, *et al.*: **Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance.** *Clin Infect Dis.* 2014; **59**(10): e150–7.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

44. F Greenhow TL, Hung YY, Herz AM, *et al.*: **The changing epidemiology of serious bacterial infections in young infants.** *Pediatr Infect Dis J.* 2014; **33**(6): 595–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

45. Byington CL, Rittichier KK, Bassett KE, *et al.*: **Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens.** *Pediatrics.* 2003; **111**(5 Pt 1): 964–8.
PubMed Abstract | Publisher Full Text

46. Sadow KB, Derr R, Teach SJ: **Bacterial infections in infants 60 days and younger: epidemiology, resistance, and implications for treatment.** *Arch Pediatr Adolesc Med.* 1999; **153**(6): 611–4.
PubMed Abstract | Publisher Full Text

47. Schrag SJ, Zywicki S, Farley MM, *et al.*: **Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis.** *N Engl J Med.* 2000; **342**(1): 15–20.
PubMed Abstract | Publisher Full Text

48. Edwards MS, Nizet V, Baker CJ: **Group B Streptococcal Infections.** In *Remington and Klein's infectious diseases of the fetus and newborn infant*, 8th ed. Elsevier/ Saunders, Philadelphia. 2016.
Reference Source

49. **Prevention of perinatal group B streptococcal disease: a public health perspective. Centers for Disease Control and Prevention.** *MMWR Recomm Rep.* 1996; **45**(RR-7): 1–24.
PubMed Abstract

50. **ACOG committee opinion. Prevention of early-onset group B streptococcal disease in newborns. Number 173--June 1996. Committee on Obstetric Practice. American College of Obstetrics and Gynecologists.** *Int J Gynaecol Obstet.* 1996; **54**(2): 197–205.
PubMed Abstract

51. **Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn.** *Pediatrics.* 1997; **99**(3): 489–96.
PubMed Abstract | Publisher Full Text

52. Schrag S, Gorwitz R, Fultz-Butts K, *et al.*: **Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC.** *MMWR Recomm Rep.* 2002; **51**(RR-11): 1–22.
PubMed Abstract

53. American College of Obstetricians and Gynecologists: **ACOG Committee Opinion: number 279, December 2002. Prevention of early-onset group B streptococcal disease in newborns.** *Obstet Gynecol.* 2002; **100**(6): 1405–12.
PubMed Abstract | Publisher Full Text

54. Committee on Infectious Diseases, American Academy of Pediatrics, Kimberlin DW, BMT, *et al.*: **Group B Streptococcal infections in Red book 2003 : report of the Committee on Infectious Diseases.** 26. ed. American Academy of Pediatrics; BMJ, Washington, D.C. London. 2003; 927.
Reference Source

55. Verani JR, McGee L, Schrag SJ, *et al.*: **Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010.** *MMWR Recomm Rep.* 2010; **59**(RR-10): 1–36.
PubMed Abstract

56. de Cueto M, Sanchez MJ, Sampedro A, *et al.*: **Timing of intrapartum ampicillin and prevention of vertical transmission of group B streptococcus.** *Obstet Gynecol.* 1998; **91**(1): 112–4.
PubMed Abstract | Publisher Full Text

57. Turrentine MA, Greisinger AJ, Brown KS, *et al.*: **Duration of intrapartum antibiotics for group B streptococcus on the diagnosis of clinical neonatal sepsis.** *Infect Dis Obstet Gynecol.* 2013; **2013**: 525878.
PubMed Abstract | Publisher Full Text | Free Full Text

58. Phares CR, Lynfield R, Farley MM, *et al.*: **Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005.** *JAMA.* 2008; **299**(17): 2056–65.
PubMed Abstract | Publisher Full Text

59. Jordan HT, Farley MM, Craig A, *et al.*: **Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis.** *Pediatr Infect Dis J.* 2008; **27**(12): 1057–64.
PubMed Abstract | Publisher Full Text

60. F Basmaci R, Bonacorsi S, Bidet P, *et al.*: ***Escherichia Coli* Meningitis Features in 325 Children From 2001 to 2013 in France.** *Clin Infect Dis.* 2015; **61**(5): 779–86.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

61. Baltimore RS, Huie SM, Meek JI, *et al.*: **Early-onset neonatal sepsis in the era of group B streptococcal prevention.** *Pediatrics.* 2001; **108**(5): 1094–8.
PubMed Abstract | Publisher Full Text

62. Edwards RK, Jamie WE, Sterner D, *et al.*: **Intrapartum antibiotic prophylaxis and early-onset neonatal sepsis patterns.** *Infect Dis Obstet Gynecol.* 2003; **11**(4): 221–6.
PubMed Abstract | Publisher Full Text | Free Full Text

63. Daley AJ, Isaacs D; Australasian Study Group for Neonatal Infections: **Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherichia coli neonatal sepsis in Australasia.** *Pediatr Infect Dis J.* 2004; **23**(7): 630–4.
PubMed Abstract | Publisher Full Text

64. Bauserman MS, Laughon MM, Hornik CP, *et al.*: **Group B Streptococcus and Escherichia coli infections in the intensive care nursery in the era of intrapartum antibiotic prophylaxis.** *Pediatr Infect Dis J.* 2013; **32**(3): 208–12.
PubMed Abstract | Free Full Text

65. Bizzarro MJ, Dembry L, Baltimore RS, *et al.*: **Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis.** *Pediatrics.* 2008; **121**(4): 689–96.
PubMed Abstract | Publisher Full Text

66. Stoll BJ, Hansen N, Fanaroff AA, *et al.*: **Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants.** *N Engl J Med.* 2002; **347**(4): 240–7.
PubMed Abstract | Publisher Full Text

67. Schrag SJ, Hadler JL, Arnold KE, *et al.*: **Risk factors for invasive, early-onset Escherichia coli infections in the era of widespread intrapartum antibiotic use.** *Pediatrics.* 2006; **118**(2): 570–6.
PubMed Abstract | Publisher Full Text

68. Moore MR, Schrag SJ, Schuchat A: **Effects of intrapartum antimicrobial prophylaxis for prevention of group-B-streptococcal disease on the incidence and ecology of early-onset neonatal sepsis.** *Lancet Infect Dis.* 2003; **3**(4): 201–13.
PubMed Abstract | Publisher Full Text

69. Puopolo KM, Eichenwald EC: **No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years.** *Pediatrics.* 2010; **125**(5): e1031–8.
PubMed Abstract | Publisher Full Text

70. F Moore AM, Ahmadi S, Patel S, *et al.*: **Gut resistome development in healthy twin pairs in the first year of life.** *Microbiome.* 2015; **3**: 27.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

71. F Gurnee EA, Ndao IM, Johnson JR, *et al.*: **Gut Colonization of Healthy Children and Their Mothers With Pathogenic Ciprofloxacin-Resistant *Escherichia coli*.** *J Infect Dis.* 2015; **212**(12): 1862–8.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

72. F Gibson MK, Wang B, Ahmadi S, *et al.*: **Developmental dynamics of the preterm infant gut microbiota and antibiotic resistome.** *Nat Microbiol.* 2016; **1**: 16024.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

73. F Gibson MK, Crofts TS, Dantas G: **Antibiotics and the developing infant gut microbiota and resistome.** *Curr Opin Microbiol.* 2015; **27**: 51–6.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

74. Gasparrini AJ, Crofts TS, Gibson MK, *et al.*: **Antibiotic perturbation of the preterm**

infant gut microbiome and resistome. *Gut Microbes.* 2016; **7**(5): 443–9.
PubMed Abstract | Publisher Full Text | Free Full Text

75. Centers for Disease Control and Prevention: **National Listeria surveillance annual summary, 2014.** 2015.
Reference Source

76. Tappero JW, Schuchat A, Deaver KA, *et al.*: **Reduction in the incidence of human listeriosis in the United States. Effectiveness of prevention efforts? The Listeriosis Study Group.** *JAMA.* 1995; **273**(14): 1118–22.
PubMed Abstract | Publisher Full Text

77. Lamont RF, Sobel J, Mazaki-Tovi S, *et al.*: **Listeriosis in human pregnancy: a systematic review.** *J Perinat Med.* 2011; **39**(3): 227–36.
PubMed Abstract | Publisher Full Text | Free Full Text

78. Jackson KA, Iwamoto M, Swerdlow D: **Pregnancy-associated listeriosis.** *Epidemiol Infect.* 2010; **138**(10): 1503–9.
PubMed Abstract | Publisher Full Text

79. Shank FR, Elliot EL, Wachsmuth I, *et al.*: **US position on *Listeria* monocytogenes in foods.** *Food Control.* 1996; **7**(4–5): 229–34.
Publisher Full Text

80. Silk BJ, Date KA, Jackson KA, *et al.*: **Invasive listeriosis in the Foodborne Diseases Active Surveillance Network (FoodNet), 2004–2009: further targeted prevention needed for higher-risk groups.** *Clin Infect Dis.* 2012; **54**(Suppl 5): S396–404.
PubMed Abstract | Publisher Full Text

81. Ventura SJ, Abma JC, Mosher WD, *et al.*: **Estimated pregnancy rates by outcome for the United States, 1990–2004.** *Natl Vital Stat Rep.* 2008; **56**(15): 1–25, 28.
PubMed Abstract

82. Lee B, Newland JG, Jhaveri R: **Reductions in neonatal listeriosis: "Collateral benefit" of Group B streptococcal prophylaxis?** *J Infect.* 2016; **72**(3): 317–23.
PubMed Abstract | Publisher Full Text

83. Dando SJ, Mackay-Sim A, Norton R, *et al.*: **Pathogens penetrating the central nervous system: infection pathways and the cellular and molecular mechanisms of invasion.** *Clin Microbiol Rev.* 2014; **27**(4): 691–726.
PubMed Abstract | Publisher Full Text | Free Full Text

84. Kim KS: **Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury.** *Nat Rev Neurosci.* 2003; **4**(5): 376–85.
PubMed Abstract | Publisher Full Text

85. F Doran KS, Fulde M, Gratz N, *et al.*: **Host-pathogen interactions in bacterial meningitis.** *Acta Neuropathol.* 2016; **131**(2): 185–209.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

86. F Liechti FD, Grandgirard D, Leib SL: **Bacterial meningitis: insights into pathogenesis and evaluation of new treatment options: a perspective from experimental studies.** *Future Microbiol.* 2015; **10**(7): 1195–213.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

87. Robinson J: **Colonization and infection of the respiratory tract: What do we know?** *Paediatr Child Health.* 2004; **9**(1): 21–4.
PubMed Abstract | Free Full Text

88. Bosch AA, Biesbroek G, Trzcinski K, *et al.*: **Viral and bacterial interactions in the upper respiratory tract.** *PLoS Pathog.* 2013; **9**(1): e1003057.
PubMed Abstract | Publisher Full Text | Free Full Text

89. Pericone CD, Overweg K, Hermans PW, *et al.*: **Inhibitory and bactericidal effects of hydrogen peroxide production by *Streptococcus pneumoniae* on other inhabitants of the upper respiratory tract.** *Infect Immun.* 2000; **68**(7): 3990–7.
PubMed Abstract | Publisher Full Text | Free Full Text

90. Margolis E, Yates A, Levin BR: **The ecology of nasal colonization of *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus*: the role of competition and interactions with host's immune response.** *BMC Microbiol.* 2010; **10**: 59.
PubMed Abstract | Publisher Full Text | Free Full Text

91. F Lysenko ES, Ratner AJ, Nelson AL, *et al.*: **The role of innate immune responses in the outcome of interspecies competition for colonization of mucosal surfaces.** *PLoS Pathog.* 2005; **1**(1): e1.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

92. F Devine VT, Jefferies JM, Clarke SC, *et al.*: **Nasopharyngeal Bacterial Carriage in the Conjugate Vaccine Era with a Focus on Pneumococci.** *J Immunol Res.* 2015; **2015**: 394368.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

93. F Ngo CC, Massa HM, Thornton RB, *et al.*: **Predominant Bacteria Detected from the Middle Ear Fluid of Children Experiencing Otitis Media: A Systematic Review.** *PLoS One.* 2016; **11**(3): e0150949.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

94. Dunne EM, Smith-Vaughan HC, Robins-Browne RM, *et al.*: **Nasopharyngeal microbial interactions in the era of pneumococcal conjugate vaccination.** *Vaccine.* 2013; **31**(19): 2333–42.
PubMed Abstract | Publisher Full Text

95. de Steenhuijsen Piters WA, Bogaert D: **Unraveling the Molecular Mechanisms Underlying the Nasopharyngeal Bacterial Community Structure.** *MBio.* 2016; **7**(1): e00009–16.
PubMed Abstract | Publisher Full Text | Free Full Text

96. Ampofo K, Bender J, Sheng X, *et al.*: **Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection.** *Pediatrics.* 2008; **122**(2): 229–37.
PubMed Abstract | Publisher Full Text

97. Sajjan U, Wang Q, Zhao Y, *et al.*: **Rhinovirus disrupts the barrier function of polarized airway epithelial cells.** *Am J Respir Crit Care Med.* 2008; **178**(12): 1271–81.
PubMed Abstract | Publisher Full Text | Free Full Text

98. Suzuki K, Bakaletz LO: **Synergistic effect of adenovirus type 1 and nontypeable Haemophilus influenzae in a chinchilla model of experimental otitis media.** *Infect Immun.* 1994; **62**(5): 1710–8.
PubMed Abstract | Free Full Text

99. Mueller JE, Gessner BD: **A hypothetical explanatory model for meningococcal meningitis in the African meningitis belt.** *Int J Infect Dis.* 2010; **14**(7): e553–9.
PubMed Abstract | Publisher Full Text

100. Bharti N, Broutin H, Grais RF, *et al.*: **Spatial dynamics of meningococcal meningitis in Niger: observed patterns in comparison with measles.** *Epidemiol Infect.* 2012; **140**(8): 1356–65.
PubMed Abstract | Publisher Full Text | Free Full Text

101. Cohen AL, McMorrow M, Walaza S, *et al.*: **Potential Impact of Co-Infections and Co-Morbidities Prevalent in Africa on Influenza Severity and Frequency: A Systematic Review.** *PLoS One.* 2015; **10**(6): e0128580.
PubMed Abstract | Publisher Full Text | Free Full Text

102. F Jansen AG, Sanders EA, VAN DER Ende A, *et al.*: **Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity?** *Epidemiol Infect.* 2008; **136**(11): 1448–54.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

103. Talbot TR, Poehling KA, Hartert TV, *et al.*: **Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation.** *Am J Med.* 2005; **118**(3): 285–91.
PubMed Abstract | Publisher Full Text

104. Kim KS: **Mechanisms of microbial traversal of the blood-brain barrier.** *Nat Rev Microbiol.* 2008; **6**(8): 625–34.
PubMed Abstract | Publisher Full Text | Free Full Text

105. Sutherland TC, Quattroni P, Exley RM, *et al.*: **Transcellular passage of *Neisseria meningitidis* across a polarized respiratory epithelium.** *Infect Immun.* 2010; **78**(9): 3832–47.
PubMed Abstract | Publisher Full Text | Free Full Text

106. Spinosa MR, Progida C, Talà A, *et al.*: **The *Neisseria meningitidis* capsule is important for intracellular survival in human cells.** *Infect Immun.* 2007; **75**(7): 3594–603.
PubMed Abstract | Publisher Full Text | Free Full Text

107. Nikulin J, Panzner U, Frosch M, *et al.*: **Intracellular survival and replication of *Neisseria meningitidis* in human brain microvascular endothelial cells.** *Int J Med Microbiol.* 2006; **296**(8): 553–8.
PubMed Abstract | Publisher Full Text

108. Magee AD, Yother J: **Requirement for capsule in colonization by *Streptococcus pneumoniae*.** *Infect Immun.* 2001; **69**(6): 3755–61.
PubMed Abstract | Publisher Full Text | Free Full Text

109. Nelson AL, Roche AM, Gould JM, *et al.*: **Capsule enhances pneumococcal colonization by limiting mucus-mediated clearance.** *Infect Immun.* 2007; **75**(1): 83–90.
PubMed Abstract | Publisher Full Text | Free Full Text

110. Weiser JN: **The pneumococcus: why a commensal misbehaves.** *J Mol Med (Berl).* 2010; **88**(2): 97–102.
PubMed Abstract | Publisher Full Text | Free Full Text

111. Turk DC: **The pathogenicity of *Haemophilus influenzae*.** *J Med Microbiol.* 1984; **18**(1): 1–16.
PubMed Abstract | Publisher Full Text

112. Stephens DS, Greenwood B, Brandtzaeg P: **Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*.** *Lancet.* 2007; **369**(9580): 2196–210.
PubMed Abstract | Publisher Full Text

113. Overturf GD: **Indications for the immunological evaluation of patients with meningitis.** *Clin Infect Dis.* 2003; **36**(2): 189–94.
PubMed Abstract | Publisher Full Text

114. Kim KS, Itabashi H, Gemski P, *et al.*: **The K1 capsule is the critical determinant in the development of Escherichia coli meningitis in the rat.** *J Clin Invest.* 1992; **90**(3): 897–905.
PubMed Abstract | Publisher Full Text | Free Full Text

115. Dietzman DE, Fischer GW, Schoenknecht FD: **Neonatal Escherichia coli septicemia--bacterial counts in blood.** *J Pediatr.* 1974; **85**(1): 128–30.
PubMed Abstract | Publisher Full Text

116. Sullivan TD, LaScolea LJ Jr, Neter E: **Relationship between the magnitude of bacteremia in children and the clinical disease.** *Pediatrics.* 1982; **69**(6): 699–702.
PubMed Abstract

117. Bell LM, Alpert G, Campos JM, *et al.*: **Routine quantitative blood cultures in children with Haemophilus influenzae or Streptococcus pneumoniae bacteremia.** *Pediatrics.* 1985; **76**(6): 901–4.
PubMed Abstract

118. Fuchs E, Untucht C, Rohde M: **Capsule Contributes to Transmigration of Streptococcus pneumoniae Serotype 7F Meningitis Isolates through Complex Blood Brain Barrier Models.** *J Bacteriol Parasitol.* 2014; **03**.
Publisher Full Text

119. Baltas I, Tsoulfa S, Sakellariou P, *et al.*: **Posttraumatic meningitis: bacteriology, hydrocephalus, and outcome.** *Neurosurgery.* 1994; **35**(3): 422–6; discussion 426-7.
PubMed Abstract | Publisher Full Text

120. Ginsberg L, Kidd D: **Chronic and recurrent meningitis.** *Pract Neurol.* 2008; **8**(6): 348–61.
PubMed Abstract | Publisher Full Text

121. van den Aardweg MT, Rovers MM, de Ru JA, *et al.*: **A systematic review of diagnostic criteria for acute mastoiditis in children.** *Otol Neurotol.* 2008; **29**(6): 751–7.
PubMed Abstract | Publisher Full Text

122. Samuel J, Fernandes CM, Steinberg JL: **Intracranial otogenic complications: a persisting problem.** *Laryngoscope.* 1986; **96**(3): 272–8.
PubMed Abstract | Publisher Full Text

123. Younis RT, Anand VK, Childress C: **Sinusitis complicated by meningitis: current management.** *Laryngoscope.* 2001; **111**(8): 1338–42.
PubMed Abstract | Publisher Full Text

124. F Simon TD, Butler J, Whitlock KB, *et al.*: **Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort study.** *J Pediatr.* 2014; **164**(6): 1462–8.e2.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

125. F Reefhuis J, Honein MA, Whitney CG, *et al.*: **Risk of bacterial meningitis in children with cochlear implants.** *N Engl J Med.* 2003; **349**(5): 435–45.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

126. Brouwer MC, de Gans J, Heckenberg SG, *et al.*: **Host genetic susceptibility to pneumococcal and meningococcal disease: a systematic review and meta-analysis.** *Lancet Infect Dis.* 2009; **9**(1): 31–44.
PubMed Abstract | Publisher Full Text

127. Kanneganti TD, Lamkanfi M, Núñez G: **Intracellular NOD-like receptors in host defense and disease.** *Immunity.* 2007; **27**(4): 549–59.
PubMed Abstract | Publisher Full Text

128. Vázquez-Boland JA, Kuhn M, Berche P, *et al.*: ***Listeria* pathogenesis and molecular virulence determinants.** *Clin Microbiol Rev.* 2001; **14**(3): 584–640.
PubMed Abstract | Publisher Full Text | Free Full Text

129. Whiteside SA, Razvi H, Dave S, *et al.*: **The microbiome of the urinary tract--a role beyond infection.** *Nat Rev Urol.* 2015; **12**(2): 81–90.
PubMed Abstract | Publisher Full Text

130. Wettergren B, Jodal U: **Spontaneous clearance of asymptomatic bacteriuria in infants.** *Acta Paediatr Scand.* 1990; **79**(3): 300–4.
PubMed Abstract | Publisher Full Text

131. Tebruegge M, Pantazidou A, Curtis N: **Question 1. How common is co-existing meningitis in infants with urinary tract infection?** *Arch Dis Child.* 2011; **96**(6): 602–6.
PubMed Abstract | Publisher Full Text

132. F Carl MA, Ndao IM, Springman AC, *et al.*: **Sepsis from the gut: the enteric habitat of bacteria that cause late-onset neonatal bloodstream infections.** *Clin Infect Dis.* 2014; **58**(9): 1211–8.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

133. F Aloisio I, Mazzola G, Corvaglia LT, *et al.*: **Influence of intrapartum antibiotic prophylaxis against group B *Streptococcus* on the early newborn gut composition and evaluation of the anti-*Streptococcus* activity of *Bifidobacterium* strains.** *Appl Microbiol Biotechnol.* 2014; **98**(13): 6051–60.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

134. Keski-Nisula L, Kyynäräinen H, Kärkkäinen U, *et al.*: **Maternal intrapartum antibiotics and decreased vertical transmission of *Lactobacillus* to neonates during birth.** *Acta Paediatr.* 2013; **102**(5): 480–5.
PubMed Abstract | Publisher Full Text

135. F Mazzola G, Murphy K, Ross RP, *et al.*: **Early Gut Microbiota Perturbations Following Intrapartum Antibiotic Prophylaxis to Prevent Group B Streptococcal Disease.** *PLoS One.* 2016; **11**(6): e0157527.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

136. F Azad MB, Konya T, Persaud RR, *et al.*: **Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study.** *BJOG.* 2016; **123**(6): 983–93.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

137. F Lim ES, Zhou Y, Zhao G, *et al.*: **Early life dynamics of the human gut virome and bacterial microbiome in infants.** *Nat Med.* 2015; **21**(10): 1228–34.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

138. F La Rosa PS, Warner BB, Zhou Y, *et al.*: **Patterned progression of bacterial populations in the premature infant gut.** *Proc Natl Acad Sci U S A.* 2014; **111**(34): 12522–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

139. Norman JM, Handley SA, Virgin HW: **Kingdom-agnostic metagenomics and the importance of complete characterization of enteric microbial communities.** *Gastroenterology.* 2014; **146**(6): 1459–69.
PubMed Abstract | Publisher Full Text | Free Full Text

140. Maródi L: **Neonatal innate immunity to infectious agents.** *Infect Immun.* 2006; **74**(4): 1999–2006.
PubMed Abstract | Publisher Full Text | Free Full Text

141. Levy O: **Innate immunity of the newborn: basic mechanisms and clinical correlates.** *Nat Rev Immunol.* 2007; **7**(5): 379–90.
PubMed Abstract | Publisher Full Text

142. Ygberg S, Nilsson A: **The developing immune system - from foetus to toddler.** *Acta Paediatr.* 2012; **101**(2): 120–7.
PubMed Abstract | Publisher Full Text

143. Burchett SK, Corey L, Mohan KM, *et al.*: **Diminished interferon-gamma and lymphocyte proliferation in neonatal and postpartum primary herpes simplex virus infection.** *J Infect Dis.* 1992; **165**(5): 813–8.
PubMed Abstract | Publisher Full Text

144. Sullender WM, Miller JL, Yasukawa LL, *et al.*: **Humoral and cell-mediated immunity in neonates with herpes simplex virus infection.** *J Infect Dis.* 1987; **155**(1): 28–37.
PubMed Abstract | Publisher Full Text

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The referees who approved this article are:

Version 1

1 **Stephen Leib**, Institute for Infectious Diseases, University of Bern, Bern, Switzerland
Competing Interests: No competing interests were disclosed.

2 **Robert Heyderman**, Division of Infection & Immunity, University College London, London, UK
Competing Interests: No competing interests were disclosed.

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Competing Interests: No competing interests were disclosed.