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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Recommended Citation

Janowski, Andrew B. and Newland, Jason G., "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*. 6, 86. (2017).  
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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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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)

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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.

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

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. 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. 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%). By 2014, in children under age 5 in the US, *S. pneumoniae* was the most frequently identified pathogen whereas *H. influenzae* was rarely detected.

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).

In 2000, a seven-valent pneumococcal vaccine (PCV7) targeting a subset of serotypes associated with invasive disease was licensed in the US. 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. 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. Substantial reductions in invasive pneumococcal infections were also observed in other countries after implementation of the PCV7 vaccine. However, surveillance data identified a rise in the incidence of meningitis caused by serotypes not included in the vaccine, known as serotype replacement, 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). However, there are conflicting data as to whether the introduction of PCV13 has decreased the rate of *S. pneumoniae* meningitis.

The dramatic reduction in the incidence of *H. influenzae* meningitis demonstrates the tremendous success of the serotype B vaccine. *H. influenzae* type B is a highly virulent strain that caused the majority of *H. influenzae* meningitis cases. 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
of meningitis per 100,000 population per year\(^2\). 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\(^{11,23,24}\).

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\(^2\). 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, meningococcaemia occurred in 0.14 cases per 100,000 persons in the US, representing a total of 443 invasive cases\(^2\). 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\(^3\). From that same study, serogroup B caused 64% of cases of meningitis, serogroup Y caused 16%, and serogroup C caused 12%\(^3\). Similar reductions in *N. meningitidis*-associated diseases have been observed in other countries after the implementation of vaccination strategies\(^{21,31,32}\). *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\(^3\). 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\(^{33,36}\).

**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\(^45-46\).

The primary reason behind the shift in the epidemiology in the US has been the implementation of intrapartum antibiotic prophylaxis against GBS\(^{47,48}\). 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\(^{49-53}\). Pregnant mothers are screened for rectovaginal colonization at 35 to 37 weeks’ gestation for GBS, and colonized mothers are provided with intrapartum antibiotic prophylaxis\(^{54-56}\). 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\(^{57}\). Efficacy of reducing transmission is enhanced if a beta-lactam or cephalexin antibiotic is given at least 4 hours prior to delivery\(^{49,57}\). This intervention has dramatically reduced the rates of early onset sepsis from GBS, including meningitis (Figure 2a)\(^{45}\). 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\(^{39}\).

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\(^{60-62}\). However,
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. The incidence of late-onset disease from *E. coli* has also increased in term or preterm infants. *E. coli* isolated from cases of meningitis is frequently resistant to ampicillin, but an increase in ampicillin-resistant *E. coli* has been observed only in low-birth-weight or premature infants. 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.

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. 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. Increased safety in food product handling was the major driving force in the reduction of cases in the US during the 1980s and 1990s. 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. and the US birth rate. 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*. 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. A total of 6.87 llisteria 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).

**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). 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. Recently, 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. 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. Increased safety in food product handling was the major driving force in the reduction of cases in the US during the 1980s and 1990s. 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. and the US birth rate. 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*. 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. A total of 6.87 llisteria 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).

**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 breaching 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. Viruses can contribute to bacterial adherence to epithelial surfaces through viral factors and upregulation of host adhesion proteins. 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. Associations between viral infection and meningitis have been observed, and these associations may partially explain outbreaks or seasonality of meningitis.

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. The capsule is an important virulence factor that confers added protection from phagocytosis, complement pathways, and penetration of the epithelium and BBB. 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.

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. 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. Other mechanisms of crossing the BBB, including paracellular pathways or the “Trojan horse” mechanism of infected phagocytes, have been identified. 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.

Upon entry of bacterial pathogens into the CNS, they rapidly divide, as the CNS is devoid of complement, antibodies, and opsonic proteins. The immune response is activated by Toll-like receptors and Nod-like receptors recognizing pathogen-associated molecular patterns. These signaling pathways lead to the production of proinflammatory cytokines and mobilization of the immune response, leading to leukocytosis of white blood cells. 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. Neuronal injury is also caused by toxic molecules released by the immune response, including reactive oxygen species, nitrous oxide, and peroxynitrite. The release of proteases and excitatory amino acids by the immune response also contributes to neurotoxicity.

**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. Late-onset sepsis is associated with a period of asymptomatic bacterial colonization and subsequent invasion. 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. 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. The second potential site of colonization is the urinary tract, which may harbor asymptomatic bacteriuria. 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.

In premature infants, bacteremic events can be preceded by colonization of the gut by the causative pathogen. 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. 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. 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. In a longitudinal study of healthy twins, the neonatal bacterial microbiome gained bacterial diversity with increased age, and conversely bacteriophage diversity decreased with age. 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.

The relatively immature immune system of the neonate also contributes to the invasive risk of bacterial pathogens. Defects in phagocytic cell function, chemotaxis, cytokine production, complement pathways, Toll-like receptor responses, and antibody production are further conducive to invasive disease. These defects also include adaptive immunity in response to viral infections, including lymphocyte proliferation and antibody responses. 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.

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**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.
Open Peer Review

Current Referee Status: ✓ ✓ ✓

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The referees who approved this article are:

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.

3 Adam Ratner, Division of Pediatric Infectious Diseases, New York University, New York, NY, 10016, USA
   Competing Interests: No competing interests were disclosed.