Changing Epidemiology of Bacterial Meningitis

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Immunization against the most common meningeal pathogens is the leading factor associated with decreased incidence of bacterial meningitis in countries where routine vaccination is available. This is most dramatically illustrated by the reduction in the incidence of *Haemophilus influenzae* type b meningitis. The incidence of bacterial meningitis has decreased by 55% since the introduction of the *H. influenzae* type b conjugate vaccine in 1990. *H. influenzae* occurred primarily in children younger than 5 years of age, and so the median age of patients with bacterial meningitis has now increased to 39 years of age in the United States, and the leading pathogen is currently *Streptococcus pneumoniae*. Three other control measures (ie, universal screening and antibiotic prophylaxis of pregnant women for Group B streptococci and the implementation and availability of the *S. pneumoniae* and *Neisseria meningitidis* conjugate vaccines) have likely further decreased the incidence of these meningeal pathogens. Lastly, the worldwide emergence of multidrug-resistant pneumococci has complicated the empiric therapy of bacterial meningitis.

Introduction

Major changes in the epidemiology of bacterial meningitis in the United States (Table 1) and in the world have changed the empirical management of patients presenting with bacterial meningitis. Before the widespread use of the *Haemophilus influenzae* type b (Hib) conjugate vaccine, Hib accounted for 70% of cases of bacterial meningitis among children younger than 5 years old [1]. In 1995, a US Centers for Disease Control and Prevention (CDC)-sponsored multistate surveillance study of cases of bacterial meningitis documented a 94% reduction in the number of cases of *H. influenzae* meningitis, and *Streptococcus pneumoniae* was the most common pathogen identified [2]. Because *H. influenzae* was, in the past, responsible for the majority of cases of bacterial meningitis in children younger than 5 years old, the median age of persons with bacterial meningitis has now increased from 15 months to 39 years of age [1–3]. In the most recent CDC surveillance study, the incidence of bacterial meningitis further decreased from 1.9 cases per 100,000 in 1998 to 1.5 cases per 100,000 in 2003 [3]. Pneumococcal meningitis among children 2 to 23 months of age decreased 65% between 1998 and 2003, most likely due to the introduction of the pneumococcal conjugate vaccine in 2000. Unfortunately, the study did not show evidence of herd immunity in the adult population. The most common etiologic agent of bacterial meningitis in the latest US surveillance study was *S. pneumoniae* (61%), followed by *Neisseria meningitidis* (16%) and group B streptococcus (14%). *H. influenzae* accounted for 7% and *Listeria monocytogenes* for only 2% of cases of bacterial meningitis.

Other factors that are changing the epidemiology of bacterial meningitis include the prevention of early neonatal group B streptococcal (GBS) disease, the emergence of multidrug-resistant pneumococci, and the availability of the conjugate meningococcal vaccines. In 2002, revised guidelines for the prevention of perinatal invasive GBS disease were issued by the CDC, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics [4,5]. In the United States, the prevalence of early-onset GBS disease decreased from two cases per 1000 live births in 1990 to 0.3 cases per 1000 in 2004. Penicillin-resistant *S. pneumoniae* now account for approximately one third of all invasive pneumococcal isolates [6]; empiric therapy of patients with suspected bacterial meningitis has been complicated, because high-level penicillin resistance is also associated with resistance to third-generation cephalosporins, which are commonly used to treat pneumococcal meningitis. Finally, in countries were the meningococcal vaccine has been implemented, reductions in the incidence of the specific serotypes of meningococcal disease have been documented. These issues will be discussed in more detail in the following sections.

Table 1. Changing epidemiology of bacterial meningitis in the United States, 1986–2003

	1986*	1995†	1998–2003‡
Meningeal pathogens			
Haemophilus influenzae	45%	7%	7%
Streptococcus pneumoniae	18%	47%	61%
Neisseria meningitides	14%	25%	16%
Group B streptococcus	5.7%	12%	14%
Listeria monocytogenes	3.2%	8%	2%
Median age	15 months	25 years	39 years
Estimated number of cases per year in the United States	12,920	5755	4450

*Data from Wenger et al. [1].
†Data from Schuchat et al. [2].
‡Data from Thigpen et al. [3].

Haemophilus influenzae type b

Prior to the advent of the Hib conjugate vaccines, Hib was the most common etiologic agent causing bacterial meningitis among children under 5 years of age. In the United States alone, Hib meningitis accounted for 45% of all cases of bacterial meningitis in 1986 [1], with the greatest burden of disease occurring in children younger than 5 years of age and serotype b accounting for 95% of cases [7].

Hib can be classified into different serotypes based on the composition of their polysaccharide capsule. The most common and virulent serotype is type b. The initial *H. influenzae* vaccine utilized the polyribosyl ribitol phosphate (PRP) component of the capsule as the immunogen [8]. Although safe and effective in adults, this vaccine provided inadequate protection for infants and children, because PRP is a T cell–independent antigen and was poorly immunogenic among the patients who were most often susceptible to invasive disease.

However, the PRP vaccines were an effectual antecedent to the next generation of vaccines that were more immunogenic by converting PRP from inducing a T cell–independent antigenic response to a T cell–dependent one. These conjugate vaccines are made up of carrier proteins covalently conjugated to the PRP [8]. Studies with the Hib conjugate vaccine demonstrated both immunogenicity and efficacy [9,10]. An unanticipated consequence of these vaccines was the reduction of nasal carriage of *H. influenzae* among children, subsequently leading to herd immunity in the population [11]. This is important, because individuals in close contact to patients with Hib are more likely to be colonized with Hib, and invasive disease is more likely to occur in such individuals. Recognizing the increased risk of invasive disease following exposure to Hib, chemoprophylaxis with rifampin has been advocated [12]. Based on the success of Hib conjugate vaccine and its reduction in the numbers of those susceptible to invasive Hib, recommendations have been modified such that chemoprophylaxis is now only recommended in those persons younger than 4 years of age who have not been fully vaccinated against Hib [13].

Almost 20 years after the first Hib conjugate vaccine was introduced, the majority of industrialized countries have adopted routine immunization into their standard childhood vaccination schedule, and the resulting effect has been striking (Table 2). In the United States, cases of Hib meningitis decreased 94% from 2.9 to 0.2 cases per 100,000 population in 10 years (1986–1996) [14]. In Finland, where the incidence of Hib meningitis had increased 130% from 1950 to 1984, introduction of the Hib conjugate vaccine resulted in an annual decline in the incidence of cases, ultimately resulting in zero cases in 1991 among children up to 4 years old [15]. In Scotland, children younger than 1 year old and from 1 to 4 years old from the time period 1983 to 1991 to the time period 1992 to 1999 had reductions of 31.2 to 3.2 cases per 100,000 and 52.2 to 12.7 cases per 100,000, respectively [16].

In nonindustrialized countries, declining rates of Hib meningitis have also been described since the introduction of the Hib conjugate vaccine. In Qatar, the raw number of cases of Hib meningitis from selected hospitals fell [17]. In Uruguay, the total number of Hib cases fell from roughly 55 per 100,000 in 1994 to five per 100,000 in 1995 [17]. In Cuba, the conjugate vaccine was introduced in 1999, and the total overall incidence of Hib meningitis fell from three per 100,000 in 1999 to 0.1 per 100,000 in 2003 [18]. Accordingly, the greatest decrease in incidence of Hib meningitis occurred in children under 5 years of age; in 1998, there were 10.7 per 100,000 cases, and in 2003, no cases were detected [18]. The Hib conjugate vaccine was introduced in the Kilifi District of Kenya in 2001. Prior to introduction of the vaccine, the incidence of invasive Hib in children under 5 years of age was 66 per 100,000 [19••] compared to an incidence of disease of 7.6 cases per 100,000 from 2004 to 2005. Vaccine effectiveness was noted to be 88% (95% CI, 73%–96%) [20–23].

In the past, because of cost, the availability of the Hib conjugate vaccine was limited to affluent countries. The impact of this vaccine has been impressive, and it has been estimated that 78% of annual cases of Hib meningitis are

Table 2. Changing trends in Hib, *Streptococcus pneumoniae*, and *Neisseria meningitides* after vaccination

Study	Country	Age, *y*	Incidence per 100,000		Decrease in incidence, %
			Prior to vaccine (year)	After vaccine (year)	
Haemophilus influenzae					
CDC [7]	USA	< 5	23 (1990)	0.3 (1998–2000)	99
Broadhurst et al. [20]	USA	< 5	91.7 (1984–1987)	45.6 (after 1987)	50
Peltola et al. [21]	Sweden	< 5	31 (1986)	1 (1987–1990)	97
Kyaw et al. [16]	Scotland	All ages	1.2 (1983–1991)	0.1 (1992–1999)	92
Cowgill et al. [19••]	Kenya	< 5	66 (2000–2001)	7.6 (2004–2005)	89
Daza et al. [22]	Malawi	< 5	20–40 (1997–2002)	0 (2003–2004)	100
Dickinson and Perez [18]	Cuba	< 18	3 (1998)	0.1 (2003)	97
Wenger et al. [17]	Qatar	NS	14 (1992)	1 (1995)	93
Peltola [23]	Uruguay	< 5	22 (1992–1993)	1 (1995-1996)	96
Streptococcus pneumoniae					
Poehling et al. [33]	USA	< 3 months	11.8 (1997–2000)	7.2 (2001–2004)	58
Whitney et al. [30]	USA	< 5	96.4 (1998–1999)	39.7 (2001)	59
		20–39*	11.2 (1998–1999)	7.6 (2001)	32
		40–64*	21.5 (1998–1999)	19.7 (2001)	8
		> 65*	60.1 (1998–1999)	49.5 (2001)	18
Kyaw et al. [36•]	USA	All ages	6.3 (1999)	2.7 (2004)	57
Abuelreish et al. [34]	USA	≤ 18	15.5 (1999)	6.5 (2002)	58†
		≤ 18	2.2 (1999)	0.4 (2002)	82‡
O'Brien and Santosham [25]	USA	< 2	113.8	38.2	66
CDC [32]	USA	< 5	80 (1998–1999)	4.6 (2003)	94
		> 65*	60.1 (1998–1999)	41.7 (2003)	31
Neisseria meningitides					
Balmer et al. [37]	UK	15–17	9.28 (1999)	3.62 (2001)	61
Ramsay et al. [42]	UK	< 18	4.08 (1998–1999)	1.36 (2001–2002)	67
Miller et al. [43]	UK	< 18	537 (1998–1999)	103 (2000–2001)	81
Brundage et al. [38]	USA	NS	23.6 (1964–1971)	1.3 (1983–1998)	94
Wahdan et al. [45]	Egypt	6–15	10.2 (1973)	1.1 (1973)	89

*Decrease in incidence in *S. pneumoniae* in unvaccinated adults could represent herd immunity.
†Incidence in 10,000 decrease in invasive pneumococcal disease.
‡Incidence in 10,000 decrease in meningitis.
CDC—US Centers for Disease Control and Prevention; Hib—*Haemophilus influenzae* type b; NS—not stated.

currently prevented [8]. Unfortunately, there are still 175 countries and 118 million children without access to the Hib conjugate vaccine, such that in many areas of the world, Hib continues to cause life-threatening disease.

Streptococcus pneumoniae

Pneumococcal vaccination

Prior to the development and use of the 7-valent protein-polysaccharide pneumococcal conjugate vaccine (PCV7), invasive pneumococcal disease (IPD) was considered a predominant cause of morbidity and mortality throughout the industrialized and nonindustrialized world [14]. IPD has superseded Hib as the most common form of invasive bacterial disease in children [9], and the burden of disease is predominately limited to the extremes of age [24,25]. Pneumococcal disease may manifest as otitis media, sinusitis, pharyngitis, bacteremia, and meningitis. Pneumococcal meningitis has been associated with greater case fatality rates than other pneumococcal diseases, and in one report, death from pneumococcal infections was greater for pneumococcal meningitis than for all others combined [24]. Moreover, intracranial complications have been described in adults with pneumococcal meningitis. In 75%

of patients in one study, complications included arterial and venous cerebrovascular complications, diffuse brain swelling, hydrocephalus, myelitis, and cerebritis [26].

S. pneumoniae is a gram-positive coccus with 90 known serotypes. The majority of disease manifestations have occurred with a limited number of serotypes, which was the basis for use of the 23-valent pneumococcal polysaccharide vaccine that has been available since the 1970s. However, this vaccine was poorly immunogenic in children and had no effect on nasopharyngeal carriage [27]. In 2000, PCV7 was introduced after randomized controlled studies proved an efficacy of 94% in the prevention of IPD in a study of 37,868 children in California [25]. The seven serotypes contained within the pneumococcal conjugate vaccine accounted for 86% of cases of bacteremia, 83% of cases of meningitis, and 65% of cases of acute otitis media from 1976 to 1994 among US children under 6 years of age [28].

The debut of the pneumococcal conjugate vaccine had an immediate effect on the incidence of IPD (Table 2) [29]. Within a year of its introduction, the rates of disease among children 2 years of age and younger fell from 188 cases per 100,000 in 1998 to 1999 to 59 cases per 100,000 in 2001 [30]. In the same study over the same period of time, children under 5 years of age experienced a 59% decrease in the rate of IPD, from 96.4 cases per 100,000 in the period from 1998 to 1999 to 39.7 per 100,000 in 2001 [30]. The same study also showed a relationship between those vaccinated and those not vaccinated, indicative of a herd immunity enjoyed by those not vaccinated. Adults 65 years and older who were not vaccinated with the conjugate pneumococcal vaccine had an 18% decrease of IPD when compared to the baseline years of 1998 to 1999; the protection conferred upon these adults was consistent with serotypes included in the conjugate vaccine and not in the 23-valent polysaccharide vaccine [30].

In a study of eight US children's hospitals after the introduction of the PCV7, a 77% decline of IPD in children 2 years of age and younger was seen in those whose serotypes of PCV7 were considered [31]. Furthermore, a 56% decrease in the incidence of meningitis was also observed in this same study [31].

The CDC evaluated the outcome of the PCV7, utilizing surveillance data from 2001 to 2003 [32]. In children under 5 years of age, the incidence of total IPD decreased 75% from 96.7 to 23.9 cases per 100,000. In the same age group, the incidence of vaccine-type IPD decreased 94% from 80 to 4.6 cases per 100,000. As with other reports, it was noted that a decrease in the incidence of IPD was observed by those aged 65 years and greater, from 33.6 cases to 11.9 cases per 100,000.

In a prospective study evaluating PCV7 in infants up to 90 days old using surveillance data from 1997 to 2004 in eight states, the authors were able to demonstrate decreases in the incidence IPD among the group who were not vaccinated with the PCV7. Among all infants in the study, there was a decrease in IPD from 11.8 cases to 7.2 cases per 100,000. Among black infants, the incidence of IPD decreased even further, from 17.1 cases to 5.3 cases per 100,000 [33].

In another study evaluating the effects of a shortage of PCV7 on the incidence of IPD, the authors demonstrated that had a shortage not occurred, a continued decline in the incidence of disease would have materialized instead of the observed slight increase in incidence of IPD [34].

Multidrug-resistant *Streptococcus pneumoniae*

The emergence of penicillin- and cephalosporin-resistant *S. pneumoniae* is now a worldwide problem. Although the first penicillin-resistant *S. pneumoniae* isolate was described in 1967, it was not until the past decade that the incidence of worldwide infection with multidrug-resistant *S. pneumoniae* has increased [6]. The resistance of *S. pneumoniae* to penicillin and other β-lactams is due to variations in the structure and molecular size of penicillin-binding proteins. In the 1995 multistate surveillance study conducted by the CDC [2], 35% (29/84) of cerebrospinal fluid isolates of *S. pneumoniae* that underwent susceptibility testing were resistant to penicillin (14% highly resistant; minimum inhibitory concentration ≥ 2 μg/mL). These changes in the resistance patterns of *S. pneumoniae* mandate in vitro susceptibility testing for all isolates and have changed the empiric approach to antimicrobial therapy in patients with bacterial meningitis. Furthermore, a recent study has shown that penicillin resistance is an independent predictor of mortality in patients with pneumococcal meningitis [35]. Fortunately, the rate of antibiotic-resistant pneumococci has decreased with the use of the conjugate vaccines [36•].

Neisseria meningitidis

N. meningitidis is the second most common cause of bacterial meningitis in the United States, accounting for 16% of all cases, and is the leading pathogen in patients 2 to 18 years of age [3]. Secondary cases can be prevented by the administration of the meningococcal vaccine and by antibiotic prophylaxis of patient contacts to those with meningococcal disease. Nasopharyngeal colonization with *N. meningitidis* occurs in 5% to 10% of the population in the United States, but invasive disease occurs in only one to two persons per 100,000. Invasive meningococcal disease occurs in patients without bactericidal or opsonizing antibodies. Meningococcal polysaccharide vaccines that induce serum bactericidal antibodies have been shown to be efficacious in controlling outbreaks and epidemics [37].

The introduction of the meningococcal polysaccharide and conjugate vaccines has had an impact on the attack rates by the specific serogroups targeted in the vaccines (Table 2). The first polysaccharide meningococcal vaccines

(monovalent C and bivalent A and C) were introduced in the 1970s and routinely used in the military, with significant reductions in the burden of disease in military recruits [38]. The first quadrivalent (A, C, Y, and W-135) meningococcal polysaccharide vaccine (MPSV4, or Menomune®-A/C/Y/W-135, Sanofi Pasteur, Lyon, France) has been available for more than 25 years [39]. Unfortunately, these vaccines are less immunogenic in children younger than 2 years old, have a T cell–independent mechanism without a booster response, and do not create herd immunity by decreasing nasopharyngeal carriage. As with *H. influenzae* and *S. pneumoniae*, serogroup A, C, Y, and W-135 meningococcal polysaccharides have been chemically conjugated to carrier proteins in an attempt to create more efficacious vaccines.

The second quadrivalent vaccine is a meningococcal conjugate vaccine effective against serogroups A, C, Y, and W135 (MCV4, or Menactra®, Sanofi Pasteur), which was approved in January 2005 for use in persons 11 to 55 years of age. These improved vaccines have shown to induce a T cell–dependent response that improves immune response in infants and leads to booster response phenomena with subsequent doses. The conjugate vaccines may also provide herd immunity by decreasing nasopharyngeal colonization [39]. Unfortunately, the quadrivalent vaccines are not effective against serogroup B, which accounts for one third of all cases of meningococcal disease in the United States and almost two thirds of cases in France [39,40]. The immunogenicity of the capsule of the serogroup B meningococcus is poor because the capsule possesses a component (polysialic acid) that is present in fetal neural tissue. Noncapsular antigens (eg, outer membrane proteins) have been investigated as targets in the prevention of meningococcal disease in outbreak settings. Other targets for vaccination against serogroup B include other outer membrane proteins, pili, exotoxins, neisserial surface protein A, and transferring-binding proteins; intranasal vaccines are also being evaluated [41].

Increasing reports of outbreaks in college dormitories have prompted the CDC Advisory Committee on Immunization Practices to recommend considering vaccination of incoming college students [41]. Other current indications for use of the meningococcal vaccination include all preadolescent children before they enter high school, microbiologists at risk of exposure to the pathogen, military recruits, people traveling to a hyperendemic area of the world (eg, sub-Saharan Africa), and people at increased susceptibility to invasive infection (eg, those with functional or anatomic asplenia or terminal complement deficiency) [39].

The most impressive reduction in cases of meningococcal disease has been observed in military recruits. The incidence of meningococcal disease has decreased from 23.6 cases per 100,000 in 1964 to 1.3 cases per 100,000 in 1998 by implementing routine vaccination of military recruits with meningococcal polysaccharide vaccines [38]. Beginning in 1999, children in the United Kingdom were immunized with the serogroup C meningococcal conjugate vaccine. Three studies done in the United Kingdom have documented a reduction in the incidence of group C meningococcal disease [42,43].

In sub-Saharan Africa, serogroup A meningococcus continues to account for the majority of the large-scale epidemics [44]. The majority of outbreaks occur in the "meningitis belt" that extends from The Gambia in West Africa to Ethiopia and Sudan in East Africa. For 30 years, serogroup A and C meningococcal polysaccharide vaccines have been used to control epidemics. In Egypt, the serogroup A polysaccharide vaccine decreased meningococcal disease from 10.2 cases per 100,000 to 1.2 cases per 100,000 [45]. The conjugate meningococcal serogroup A and C vaccine has been studied in African infants and was shown to be effective [46]. Unfortunately, little progress has been made in the last 30 years in further developing and implementing meningococcal vaccination in Africa. However, GlaxoSmithKline (Middlesex, UK) is developing a heptavalent vaccine containing diphtheria, pertussis, and tetanus; hepatitis B; Hib polysaccharide; and group A and C meningococcal conjugates. In addition, the Bill and Melinda Gates Foundation (Seattle, WA) supports the Meningitis Vaccine Programme in India, which is developing a monovalent meningococcal conjugate vaccine for use in Africa [45].

Group B Streptococcus

GBS, also referred as *Streptococcus agalactiae*, frequently colonizes the gastrointestinal, genitourinary, and vaginal tracts. It is an important cause of pneumonia, septicemia, and meningitis in the early neonatal period after exposure to colonized vaginal secretions. GBS can also cause septicemia in pregnant women, immunocompromised patients, and the elderly [47]. During the 1990s, the incidence of neonatal GBS disease declined due to the introduction of intrapartum antibiotic prophylaxis with penicillin [5]. Stoll et al. [48] compared the microbiology of early neonatal sepsis between the periods of 1991 to 1993 and 1998 to 2000 when GBS surveillance and antibiotic prophylaxis were done routinely. They observed a reduction in the incidence of GBS neonatal sepsis, although it was at a cost of increased *Escherichia coli* infections with little net reductions in overall early-onset neonatal sepsis. Significant progress has been made in developing effective GBS vaccines that could further decrease the incidence of GBS neonatal sepsis without the concomitant increase in *E. coli* sepsis.

In 2002, revised guidelines were issued by the CDC, the American College of Obstetrics and Gynecology, and the American Academy of Pediatrics for the prevention of perinatal GBS invasive disease [4]. These guidelines recommend universal screening for rectovaginal colonization in pregnant women at 35 to 37 weeks gestation and intrapartum antibiotic prophylaxis. After these recom-

mendations, the prevalence of early-onset GBS disease decreased from two cases per 1000 live births in 1990 to 0.3 cases per 1000 live births in 2004 [49].

A current active area of research that could further change the epidemiology of GBS is the development of an effective vaccine. The current vaccines being evaluated are based on the GBS serotypes and on multilocus sequence types prevalent in the United States and Europe. Unfortunately, these vaccines are not as efficacious in other parts of the world because of different serotypes and sequence types [49].

Listeria monocytogenes

L. monocytogenes should always be considered in patients with meningitis who have cellular immunodeficiency or are at the extremes of age (ie, younger than 3 months and older than 50 years) [2]. This is very important because third-generation cephalosporins used in empiric therapeutic regimens are not active against *Listeria*, and high-dose ampicillin should be added to the empiric regimen if this pathogen is suspected. In the penicillin-allergic patient, trimethoprim-sulfamethoxazole should be used because of its bactericidal activity against *Listeria*, good cerebrospinal fluid penetration, and clinical effectiveness [50].

L. monocytogenes is one of the least common meningeal pathogens in the United States, accounting for only 2% of all cases of bacterial meningitis [3]. In the non-neonatal period, the more common predisposing conditions for *L. monocytogenes* meningitis include malignancies, transplantation, alcoholism, liver disease, steroid use, HIV infection, diabetes mellitus, and old age [50]. Even though HIV-positive patients are more likely to develop *Listeria* meningoencephalitis compared to the general population, the incidence in AIDS patients is much lower than expected [50], perhaps as a result of widespread use of trimethoprim -sulfamethoxazole prophylaxis. Other preventive measures that can reduce the possibility of acquiring listeriosis include avoiding consumption of unpasteurized dairy products or juices, cooking animal products thoroughly, and washing vegetables before consumption. No licensed vaccines exist to prevent *Listeria* infection.

Conclusions

Reductions in the incidence of the three most important meningeal pathogens (Hib, *S. pneumoniae*, and *N. meningitidis*) have been accomplished with the implementation of polysaccharide and conjugate vaccines. Meningococcal meningitis has been almost eliminated in military recruits, and countries that have implemented routine vaccinations have been very successful in reducing the attack rates of this important disease. Implementation of guidelines for group B streptococcal surveillance and antibiotic prophylaxis in pregnancy have also had a positive impact, with lower rates of early-onset invasive disease. The future challenge in this field will be to make these vaccines and other preventive strategies available to the most vulnerable populations in the underdeveloped world.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wenger JD, Hightower AW, Facklam RR, et al.: **Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group.** *J Infect Dis* 1990, **162:**1316–1323.
2. Schuchat A, Robinson K, Wenger JD, et al.: **Bacterial meningitis in the United States in 1995. Active Surveillance Team.** *N Engl J Med* 1997, **337:**970–976.
3. Thigpen MC, Rosenstein N, Whitney C, et al.: **Bacterial meningitis in the United States: 1998-2003** [abstract #65]. *Presented at the 43rd Annual Infectious Diseases Society Meeting.* San Francisco; October 9, 2005.
4. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A: **Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC.** *MMWR Morb Mortal Wkly Rep* 2002, **51(RR-11):**1–22.
5. Kainer M, McCauley T, Craig AS: **Prevention of early-onset group B streptococcal disease in newborn.** *Tenn Med* 2005, **98:**232–233.
6. Ruhe J, Myers L, Mushatt D, Hasbun R: **High-level penicillin-nonsusceptible Streptococcus pneumoniae bacteremia: identification of a low-risk subgroup.** *Clin Infect Dis* 2004, **38:**508–514.
7. Centers for Disease Control and Prevention (CDC): **Progress toward elimination of Haemophilus influenzae Type b invasive disease among infants and children—United States, 1998-2000.** *MMWR Morb Mortal Wkly Rep* 2002, **51:**234–237.
8. 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:**302–317.
9. Black SB, Shinefield HR, Fireman B, et al.: **Efficacy in infancy of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pediatrics Group.** *Pediatr Infect Dis J* 1991, **10:**97–104.
10. Santosham M, Wolff M, Reid R, et al.: **The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitides outer-membrane protein complex.** *N Eng J Med* 1991, **324:**1767–1772.
11. Takala AK, Eskola J, Leinonen M, et al.: **Reduction of oropharyngeal carriage of Haemophilus influenzae type b (Hib) in children immunized with an Hib conjugate vaccine.** *J Infect Dis* 1991, **164:**982–986.
12. Centers for Disease Control and Prevention (CDC): **Prevention of Haemophilus influenzae type b disease.** *MMWR Morb Mortal Wkly Rep* 1986, **35:**170–174, 179–180.
13. **Recommendations for the use of Haemophilus influenzae b conjugate vaccines and a combined diphtheria, tetanus, pertussis, and Haemophilus b vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR Morb Mortal Wkly Rep* 1993, **42(RR-13):**1–15.
14. Clark SC: **Control of pneumococcal disease in the United Kingdom—the start of a new era.** *J Med Microbiol* 2006, **55:**975–980.

15. Peltola H, Kilpi T: **Rapid disappearance of Haemophilus influenzae type b meningitis after routine childhood immunisation with conjugate vaccines.** *Lancet* 1992, **340:**592–594.
16. Kyaw M, Christie P, Jones I, Campbell H: **The changing epidemiology of bacterial meningitis and invasive non-meningitic bacterial disease in Scotland during the period of 1983-99.** *Scand J Infect Dis* 2002, **34:**289–298.
17. Wenger JD, DiFabio J, Landaverde JM, et al.: **Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries.** *Vaccine* 1999, **18:**736–742.
18. Dickinson FO, Perez A: **Bacterial meningitis in children and adolescents: an observational study based on the national surveillance system.** *BMC Infect Dis* 2005, **5:**103.
19.•• Cowgill KD, Ndiritu M, Nyiro J, et al.: **Effectiveness of Haemophilus influenzae type b conjugate vaccine introduction into routine childhood immunization in Kenya.** *JAMA* 2006, **296:**671–678.
The importance of this paper cannot be underestimated. Nonindustrialized nations benefiting from Hib conjugate vaccine may have a favorable influence on funding agencies.
20. Broadhurst LE, Erickson RL, Kelley PW: **Decreases in invasive Haemophilus influenzae diseases in US Army children, 1984 through 1991.** *JAMA* 1993, **269:**227–231.
21. Peltola H, Aavitsland P, Hansen KG, et al.: **Perspective: a five-country analysis of the impact of four different Haemophilus influenzae type b conjugates and vaccination strategies in Scandinavia.** *J Infect Dis* 1999, **179:**223–229.
22. Daza P, Banda R, Misoya K, et al.: **The impact of routine infant immunization with Haemophilus influenzae type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence.** *Vaccine* 2006, **24:**6232–6239.
23. Peltola H: **Haemophilus influenzae type b disease and vaccination in Latin America and the Caribbean.** *Pediatr Infect Dis J* 1997, **16:**780–787.
24. Robinson KA, Baughman W, Rothrock G, et al.: **Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era.** *JAMA* 2001, **285:**1729–1735.
25. O'Brien KL, Santosham M: **Potential impact of conjugate pneumococcal vaccines on pediatric pneumococcal diseases.** *Am J Epidemiol* 2004, **159:**634–643.
26. Kastenbauer S, Pfister HW: **Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases.** *Brain* 2003, **126:**1015–1025.
27. Segal S, Pollard AJ: **Vaccines against bacterial meningitis.** *Brit Med Bull* 2004, **72:**65–81.
28. Centers for Disease Control and Prevention (CDC): **Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP).** *MMWR Morb Mortal Wkly Rep* 2000, **49(RR09):**1–38.
29. Shinefield HR, Black S. **Efficacy of pneumococcal conjugate vaccines in large scale field trials.** *Pediatr Infect Dis J* 2000, **19:**394–397.
30. Whitney CG, Farley MM, Hadler J, et al.: **Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine.** *N Eng J Med* 2003, **348:**1737–1746.
31. Kaplan SL, Mason EO, Wald ER, et al.: **Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine.** *Pediatrics* 2004, **113:**443–449.
32. Centers for Disease Control and Prevention (CDC): **Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998-2003.** *MMWR Morb Mortal Wkly Rep* 2005, **54:**893–897.
33. Poehling KA, Talbot TR, Griffin MR, et al.: **Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine.** *JAMA* 2006, **295:**1668–1674.
34. Abuelreish M, Subedar A, Chiu T, et al.: **Increase in invasive pneumococcal disease in children associated with shortage of heptavalent pneumococcal conjugate vaccine.** *Clin Pediatr (Phila)* 2007, **46:**45–52.
35. Auburtin M, Wolff M, Charpentier J, et al.: **Detrimental role of delayed antibiotic administration and penicillin-non-susceptible strains in adult intensive care unit patients with pneumococcal meningitis: the PNEUMOREA prospective multicenter study.** *Crit Care Med* 2006, **34:**2758–2765.
36.• Kyaw MH, Lynfield R, Schaffner W, et al.: **Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumonia.** *N Engl J Med* 2006, **354:**1455–1463.
This study documents the decrease in incidence of antibiotic-resistant invasive pneumococcal disease in children and the elderly. Interestingly, an increase was seen in disease caused by a serotype not included in the vaccine.
37. Balmer P, Borrow R, Miller E: **Impact of meningococcal C conjugate vaccine in the UK.** *J Med Microbiol* 2002, **51:**717–722.
38. Brundage, JF, Ryan MA, Feighner BH, Erdtmann FJ: **Meningococcal disease among United States military service members in relation to routine uses of vaccines with different serogroup-specific components, 1964-1998.** *Clin Infect Dis* 2002, **35:**1376–1381.
39. Gardner P: **Prevention of meningococcal disease.** *N Engl J Med* 2006, **355:**1466–1473.
40. Antignac A, Ducos-Galand M, Guiyole A, et al.: **Neisseria meningitides strains isolated from invasive infections in France (1999-2002): phenotypes and antibiotic susceptibility patterns.** *Clin Infect Dis* 2003, **37:**912–920.
41. Rosenstein NE, Perkins BA, Stephens DS, et al.: **Meningococcal disease.** *N Engl J Med* 2001, **344:**1378–1388.
42. Ramsay ME, Andrews NJ, Trotter CL, et al.: **Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis.** *BMJ* 2003, **326:**365–366.
43. Miller E, Salisbury D, Ramsay M: **Planning, registration, and implementation of an immunization campaign against meningococcal serogroup C disease in the UK: a success story.** *Vaccine* 2001, **20(Suppl 1):**S58–S67.
44. Greenwood B: **Editorial: 100 years of epidemic meningitis in West Africa-has anything changed?** *Trop Med Int Health* 2006, **11:**773–780.
45. Wahdan MH, Sallam SA, Hassan MN, et al.: **A second controlled field trial of a serogroup A meningococcal polysaccharide vaccine in Alexandria.** *Bull World Health Organ* 1977, **55:**645–651.
46. Twumasi PA, Kumah S, Leach A, et al.: **A trial of a group A plus group C meningococcal polysaccharide-protein conjugate vaccine in African infants.** *J Infect Dis* 1995, **171:**632–638.
47. Dunne DW, Quagliarello V: **Group B streptococcal meningitis in adults.** *Medicine (Baltimore)* 1993, **72:**1–10.
48. 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:**240–247.
49. Johri A, Paoletti LC, Glaser P, et al.: **Group B Streptococcus: global incidence and vaccine development.** *Nat Rev Microbiol* 2006, **4:**932–942.
50. Mylonakis E, Hohmann EL, Calderwood SB: **Central nervous system infection with Listeria monocytogenes. 33 years' experience at a general hospital and review of 776 episodes from the literature.** *Medicine (Baltimore)* 1998, **77:**313–336.