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Vaccines to Prevent Bacterial Meningitis in Children

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1. Introduction

Vaccines are among the most effective public health interventions available. Global eradication of smallpox infection, the elimination of polio from the Western hemisphere, and dramatic reductions in diseases like diphtheria, tetanus, pertussis, measles, mumps, rubella, varicella, rotavirus, hepatitis A and B have all been achieved through immunization programs. The public health impact of well-structured immunization programs is well appreciated, but logistic and financial obstacles can interfere with vaccine availability and delivery. The frequency and severity of bacterial meningitis in children has also been favorable impacted by the widespread use of vaccines in all areas of the world where resources have allowed them to be implemented since the three most common causes of childhood meningitis, Haemophilus influenzae type B (HIB), pneumococcus, and meningococcus, are now, at least partially, vaccine preventable. In developed countries of the world, vaccines for all three of these bacterial infections are now considered the standard of care. Substantial progress is also being made in resource poor countries where, slowly and surely, the public health impact of immunization programs is being appreciated and international assistance to provide the money and knowledge needed for widespread vaccine delivery is being realized.

Bacterial meningitis is a life threatening infection that occurs in all age groups but disproportionately affects infants and young children. Most cases of bacterial meningitis result from hematogenous seeding of the meninges during a bloodstream infection. Direct extension of a bacterial infection from the sinuses, middle ear, or mastoid represent other routes of meningeal seeding. The most common microbiologic causes of bacterial meningitis differ based on the age of the affected patient. Common etiologic agents of bacterial meningitis in the first week of life include Streptococcus agalactiae (group B Streptococcus), Escherichia coli, and Listeria monocytogenes. Sadly, vaccines to prevent infections caused by these agents have remained elusive, although some progress has been made with experimental vaccines against group B streptococcus. Late-onset neonatal meningitis occurs after the first week of life and up to three months of age and may be caused by the agents listed above, other enteric gram negative bacilli, Pasteurella after animal exposure, pneumococci, meningococci, and staphylococci.

During later infancy and early childhood, S. pneumoniae and N. meningitidis, account for 80% of cases of bacterial meningitis in developed countries. Many of these infections are now vaccine preventable. The remaining 20% are caused by L. monocytogenes, Streptococcus pyogenes (group A strep) S. agalactiae (group B strep), H. influenzae (type B and nontypeable isolates), E. coli and other enteric gram negative rods (including salmonella species). Among these agents, only H. influenzae type B vaccines have been successful. Bacterial meningitis in adolescents and younger adults is usually caused by either S. pneumoniae or N. meningitides, however after the age of 50 years, L. monocytogenes becomes more prevalent. In elderly individuals, S. pneumoniae, N. meningitidis and L. monocytogenes remain the more common microbiologic etiologies, however a broad array of other pathogens have been described depending on the presence of co-morbidities, travel, and unusual exposures.

At present, bacterial meningitis is most common in children, particularly those living in under-developed countries of the world. In some parts of Africa, 1 in 250 children developing meningitis during their first year of life (Greenwood, 1987; Scarborough et al., 2007, Scarborough & Thwaites, 2008), and while epidemiologic surveys from the United States, Europe, Brazil, Israel and Canada show that bacterial meningitis is less common in developed parts of the world, infections are typically caused by the same bacterial species in all geographic areas. As noted, safe and effective vaccines have been developed to prevent infections caused by the three most common agents of bacterial meningitis in children—Haemophilus influenzae type B (HIB), Streptococcus pneumoniae, and Neisseria meningitidis. The introduction and implementation of these vaccines have had dramatic effects on the incidence of bacterial meningitis in all areas of the world where they have been successfully introduced, but challenges remain.

Obstacles to the prevention of bacterial meningitis in resource poor areas of the world relate to the cost of the vaccines, and the lack of solid infrastructure to store and deliver the vaccines to those most in need. A growing, and somewhat unanticipated barrier to vaccine coverage rates in developed countries has been a loss of public confidence in the safety of routine immunizations to the extent that immunization coverage rates are not as high as we have once achieved successfully. Even in countries where vaccine coverage remains excellent, cases of pneumococcal and/or meningococcal meningitis can still occur, as not all serotypes of these organisms are included in present day vaccines. For the most common causes of bacterial meningitis, vaccines are indeed available for the predominate serotypes, but since vaccines do not exist for every known serotype, cases will still be seen. This is especially important for Neisseria meningitidis serotype B, a common cause of meningitis in young infants. Moreover, the common etiologic agents affecting newborns (Escherichia coli and Streptococcus agalactiae, also commonly referred to as group B strep) and less common causes of bacterial meningitis in older children (Listeria monocytogenes, Staphylococcus aureus, Streptococcus pyogenes, and Salmonella species) are not currently preventable through licensed vaccines.

2. Available licensed vaccines for the prevention of bacterial meningitis

2.1 HIB vaccines

Haemophilus influenzae type B is an encapsulated pleiomorphic gram negative rod that causes bacteremia, sepsis, pneumonia, facial cellulitis, epiglottitis, and meningitis. Before the

mid 1980's, HIB caused roughly 20,000 cases of invasive disease per year in the U.S. alone. Almost all of these infections occurred in children under five years of age, and half of these infections were meningitis, making HIB the most common cause of bacterial meningitis in children at the time, and identifying HIB disease as a logical target for vaccine development. Other capsular serotypes, and non-typeable strains of H. influenzae are less common causes of invasive infection, but non-type B cases of meningitis are still encountered on a regular basis.

2.1.1 Early HIB vaccine efforts

In 1985, the first HIB vaccines were licensed for use in the United States for children beginning at age two years. The original formulations of the vaccine were pure polysaccharide, had an efficacy of 55-92%, and was well tolerated. Three vaccines were licensed—Praxis introduced b-Capsa-1, Lederle introduced Hib-imune; and Connaught introduced Hibvax. At the time, this was a major advance in pediatric vaccination since HIB was the most common cause of meningitis in children under five years of age, and carried a significant morbidity and mortality. Many of the infected children developed profound sensorineural hearing loss as a complication of developing meningitis, others suffered developmental and cognitive deficits, and some died. In the early days of HIB vaccine, there was controversy regarding the overall value of routine immunization, especially since the early formulations of vaccines were not effective in infants. Although it was a start, the strategy that employed the use of pure polysaccharide vaccines was suboptimal for the prevention of invasive HIB infection for several additional reasons. First, polysaccharide vaccines are not immunogenic in patients under two years of age, the age group at highest risk for HIB disease. Second, polysaccharide immunogens are processed by the immune system in a T-cell independent manner. In the absence of T-cell engagement, immunity cannot be effectively boosted with subsequent doses of vaccine. B cells are certainly stimulated to produce antibodies, but the effect is relatively short lived, and antibody titers wane over the period of several years. An absence of T-cell help impairs the durability of the immune response. Five years following receipt of a polysaccharide vaccine, the humoral evidence of prior vaccination (and immunity), is reduced or no longer detected. Third, serial re-administration of polysaccharide vaccines to individuals at any age, particularly if done so at closely spaced intervals, leads to lower antibody titers than the first dose. This phenomenon, known as 'hypo-responsiveness' remains a major limitation for the use of any pure polysaccharide vaccine.

2.1.2 Solving the problems of polysaccharides vaccines

Clinical vaccine research suggested early on that the limitations associated with the use of polysaccharide immunogens could be overcome through the use of an elegant biochemical trick. The same polysaccharide antigens used in the original HIB vaccines were covalently linked to a simple peptide. Peptides that have been used successfully in this manner include tetanus and diphtheria toxoids, the outer membrane protein of Neisseria menigitidis, and CRM197 (cross reacting material 197, a protein similar to naturally occurring diphtheria toxin). The presence of such a peptide altered the manner in which the immune system processed the antigen, specifically with regard to T-cell engagement, and allowed the vaccine to induce a robust immune response in children as young as six weeks of age. Serial doses provide additional protection and higher antibody concentrations, and booster doses

show clear evidence of immune memory. The technique whereby polysaccharide antigens are biochemically linked to a peptide produces a 'conjugate' vaccine. Table 1 shows examples of polysaccharide and conjugate vaccines made by different manufacturers, the conjugate protein used to develop them, and the year each was introduced in the United States. The successful development of conjugate HIB vaccines paved the way for the development of several other conjugate vaccines, including those currently in use for the prevention of both pneumococcal and meningococcal infections. Early pure polysaccharide, and later generation conjugate vaccines for all three types of infection are included in the Table.

Vaccine	Trade name	Manufacturer	Immunogens	Conjugate protein	Introduced in the U.S.
HIB	B-Caspa-1 Hib-Imune Hibvax	Praxis Lederle Connaught	PRP PRP PRP	None	1985, no longer used
	HIBTITER	Wyeth	HbOC	CRM197	1990, no longer used
	PedvaxHIB	Merck	PRP	OMP N. meningitidis	1989
	ActHIB	Sanofi Pasteur	PRP	Tetanus toxoid	1993
	OmniHIB	GlaxoSmithKline	PRP	Tetanus toxoid	1993, no longer used
	ProHIBIT	Connaught	PRP	Diphtheria toxoid	1987, no longer used
	Hiberix	GlaxoSmithKline	PRP	Tetanus toxoid	2010
Pneumococcal	Pneumovax	Merck	14 valent	None	1977, no longer used
	Pneumovax 23	Merck	23 valent*	None	1983
	Prevnar	Pfizer	4, 6B, 9V, 14, 18C, 19F, 23F	CRM197	2000
	Prevnar 13	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM 197	2010
Memingococcal	Menomune	Sanofi Pasteur	A, C, Y, W135	None	1981
	Menactra	Sanofi Pasteur	A, C, Y, W135	Diphtheria toxoid	2005
	Menveo	Novartis	A, C, Y, W135	CRM197	2010

*1, 2, 3, 4, 5, 6B , 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
Abbreviations: PRP (polyribosylribitol phosphate), CRM (cross reacting material), OMP (outer membrane protein), HbOC (Haemophilus B oligosaccharide conjugate)

Table 1. Vaccines to Prevent HIB, Pneumococcal and Meningococcal Infections in the United States

With the introduction of conjugate HIB vaccine during the late 1980s throughout the U.S. and other developed countries, rates of all cause bacterial meningitis fell dramatically along with the observation that the mean age at presentation from any cause of bacterial meningitis went from 15 mos in 1986 to 25 years in 1995 (Schuchat et al., 1997; Berg et al., 1996; Giorgi Rossi et al., 2009; Mishal et al., 2008; Theodoridou et al., 2007; Urwin et al., 1994; Weiss et al., 2001; Schlech et al., 1985 Wenger et al., 1990). This age shift was a direct effect of near complete elimination of HIB meningitis in the under five-year old age group. This is perhaps the most notable recent, and publically under-recognized vaccine success story of recent years. Once a cause of approximately 10,000 cases of bacterial meningitis in children every year in the U.S. alone, there is currently an average of fewer than 100 cases of invasive HIB disease reported annually.

HIB vaccine programs are among the most effective modern public health interventions of the 20th century. Pediatric cases seen in the U.S. in the present day are almost always described in unvaccinated, under-vaccinated, or immune deficient patients. When invasive HIB disease is discovered in a vaccinated child, testing should always be performed to determine if that child has an immune deficiency. The HIB success story is mirrored across the globe in areas where resources have permitted widespread introduction of vaccine to children. These results are clear and impressive. In every area of the world where vaccine programs are initiated, HIB disease, including HIB meningitis, virtually disappears.

The public health benefits of HIB vaccination have not been realized in all corners of the globe, however. Delivery of HIB and other vaccines to resource challenged areas of the world remains suboptimal. Globally, it is estimated that about 38% of infants have HIB vaccine available to them, but progress in improving this percentage is steady. Even 38% of the worlds' children translates to roughly 130,000 lives saved annually from pneumonia and meningitis caused by HIB. In the last decade alone, combined efforts on the part of the World Health Organization, UNICEF, the Bill and Melinda Gates Foundation, and other international agencies have led to more vaccine availability in the areas of the world that still need it the most. In 1997, 29 countries were using conjugate HIB vaccine, but by 2009, 161 countries had introduced it. To date, 29 countries are still without access to HIB vaccine for infants, and the epidemiology of HIB infection in those areas remains similar to the problem seen in the U.S. prior to 1985. While there has been progress in Africa and some parts of Asia, significant effort, education, and resources are still needed in the underdeveloped world to prevent this form of meningitis.

2.2 Pneumococcal vaccines

Streptococcus pneumoniae are encapsulated gram positive diplococci that continue to cause invasive infections at all ages. Of the 92 different pneumococcal serotypes (grouped into 46 serogroups based on immunologic similarities) that have been identified based on antigenic differences in their capsular polysaccharides, ten serogroups account for most of the pediatric invasive pneumococcal infections worldwide with serogroups 1, 3, 6, 14, 19 and 23 being the most common. Pneumococci commonly infect the sinopulmonary tract causing otitis media, sinusitis, and pneumonia. Bacteremia with sepsis is not uncommon. Meningeal seeding, with a resulting bacterial meningitis can occur at any age, including previously healthy individuals, and patients with defined risk factors, including immune deficiency, HIV infection, asplenia, hemoglobinopathies, diabetes and alcoholism. Worldwide, S.

pneumoniae remains the most common cause of bacterial meningitis identifying it as an important target for vaccine development.

2.2.1 Early vaccine development

Vaccines designed to prevent invasive pneumococcal disease were available in the early 1900s, but early goals were focused primarily in the prevention of lower respiratory tract infection in adults. Two hexavalent vaccines were licensed for use in adults after World War II, but with the emerging availability of antibiotics, enthusiasm for the use of vaccines to prevent disease waned. In the absence of public demand, the vaccines were removed from the market. Interest in the prevention of pneumococcal infections re-emerged in the 1960s. A 14-valent pure polysaccharide vaccine was licensed for use in adults in 1977, ultimately being replaced by a new generation polysaccharide 23-valent vaccine in 1983. The 23-valent polysaccharide vaccine, which is still available, was FDA licensed in the United States in 1983 for use in adults and high-risk children older than 2 years. Its role has been primarily to prevent pneumococcal pneumonia in high-risk adults. Its major limitation as a pure polysaccharide vaccine (it is not a conjugate vaccine) is that it is poorly immunogenic in young children. Like other polysaccharide vaccines, it is processed by the immune system in a T-cell independent manner so the duration of immune protection is brief, and there is no potential for boosting with subsequent doses.

In 2000, a heptavalent pneumococcal vaccine, Prevnar, was added to the universal pediatric immunization schedule in the U.S. resulting in an almost immediate reduction in invasive pneumococcal infections, including a reduction in cases of meningitis. U.S. population-based data from the Active Bacterial Core Surveillance was published in 2003 showing a 59% decline in pneumococcal meningitis in young children (Whitney et al., 2003), and Nationwide Inpatient Service data showed that the incidence rate fell by 33% in children less than 5 years of age (from 0.8 to 0.55 cases per 100,000 population) (Tsai et al., 2008).

The power of national surveillance, coupled with the impressive efficacy of pneumococcal vaccine illustrated the public health benefits in just three years following vaccine introduction. When it is appreciated that Prevnar was in somewhat short supply during much of those early years, the dramatic beneficial effect becomes even more obvious. The majority of children in the U.S. during 2000-2002 received a 3-dose primary vaccine series, but an Advisory Committee on Immunization Practices recommendation to defer the booster fourth dose until supplies were available led to substantial delays in the timeliness of completing the four dose series. Despite this difficulty with timeliness to vaccine series completion, the public health impact of conjugate vaccine was almost immediately recognized through surveillance networks.

The heptavalent (7-valent) pneumococcal vaccine Prevnar included conjugated pneumococcal polysaccharide antigens against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. At the time of licensure, these capsular types were the most likely to cause invasive infection in children in the Unites States. Serotype prevalence varies somewhat according to world geography, but for the most part, the same types are responsible for invasive infection in most of the world. As conjugate pneumococcal vaccine was being developed, another public health problem related to infections caused by S. pneumoniae had already become well recognized. Strains of S. pneumoniae had gradually emerged that were less and less

susceptible to penicillin. Treatment of pneumococcal infections with penicillin or other beta-lactam antibiotics was no longer 'guaranteed' to eradicate infection. This problem impacted empiric management of mild to moderate infections such as otitis media and pneumonia, but also raised serious concerns about how to best manage empiric antibiotics in serious and life-threatening infections such as meningitis.

As antibiotic resistance increased in pneumococci, moderate and severe infections began to be managed with different antimicrobial regimens. Penicillin treatment of severe disease was used only after antimicrobial susceptibility profiles were confirmed. The problem was not isolated to the use of penicillin, as the mechanism of penicillin resistance in S. pneumoniae depends on a series of mutations in its penicillin binding proteins (PBPs) that also alter the antimicrobial susceptibility to all beta lactam antibiotics. It should be understood that this mechanism of antibiotic resistance does not depend on the production of a beta-lactamase enzyme, and that beta lactamase producing S. pneumoniae isolates have not ever been described. Instead, antibiotic pressure has led some strains of S. pneumoniae to alter their PBPs so that their affinity for penicillin is reduced. When this occurs, the penicillin can no longer bind to and inhibit the transpeptidase activity of the PBP, a function that is necessary for peptidoglycan cross linking. This biochemical alteration becomes obvious in the laboratory as gradual increases in the minimal inhibitory concentrations (MICs) of penicillin, and ultimately in the observation that the organism is 'intermediate' or 'resistant' to penicillin. As penicillin resistant strains gain additional mutations in these PBPs, the MICs to all beta lactam antibiotics begin to increase. MICs to first, then second, and then to third generation cephalosporins increase. Pneumococci that are resistant to advanced generation cephalosporins like cefotaxime and ceftriaxone are now encountered on a regular basis. The emergence of these resistant strains has led to a change in how bacterial meningitis is treated empirically, where a third generation cephalosporin (ceftriaxone or cefotaxime) in combination with vancomycin is typically used until antimicrobial susceptibility profiles are known. The rationale for incorporating vancomycin into the empiric regimen is to be sure that every patient with pneumococcal meningitis has effective antimicrobial therapy initiated at the time that meningitis is suspected. When the microbiology laboratory confirms that the infection is caused by S. pneumoniae, and that the infecting organism is susceptible to penicillin or a third generation cephalosporin, the treatment can be 'de-escalated' to the appropriate antibiotic.

One of the under-appreciated benefits of introducing the conjugate pneumococcal vaccine in the U.S. in 2000 was the observation that the original seven conjugate vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were among the most likely to be penicillin resistant. This offered the potential to reduce infection caused by the most prevalent pneumococci, while at the same time reduce the possibility that infections would be caused by antibiotic resistant strains. During the decade following introduction of the 7-valent conjugate vaccine, there was a substantial reduction in invasive pneumococcal infections reported in children, including meningitis, but a troubling pattern began to emerge in the form of nonvaccine replacement serotypes. Like early prevalent pneumococcal serotypes, several of these replacement types were resistant to beta lactam antibiotics.

In 2010, the heptavalent pneumococcal vaccine was replaced with a newly developed 13-valent vaccine (by the same manufacturer) to expand the number of covered serotypes. The new generation 13-valent vaccine became available in 2010, and was immediately

recommended as a replacement for the 7-valent vaccine. The additional serotypes included 1, 3, 5, 6A, 7F, and 19A. The inclusion of serotypes 6A and 19A are of particular importance in this new generation vaccine as these capsular types were the ones that emerged as the most serious replacement serotypes during the successful decade following introduction of the heptavalent vaccine. Serotype 19A remains a serious threat. Some infections caused by this strain are highly resistant to all penicillins, cephalosporins, and carbapenems making treatment for infections of the central nervous system challenging. In such situations, treatment with vancomycin and/or lineazolid has been successful. As experience with and implementation of the 13 valent conjugate vaccine continues, an optimistic possibility is that infections caused by the most difficult-to-treat pneumococcal strains will diminish. The possibility that new serotypes could emerge as novel replacement serotypes remains a threat, highlighting the need for ongoing surveillance.

Like HIB vaccines, conjugate pneumococcal vaccines are not available in all parts of the world. In the developing world, invasive pneumococcal disease remains the 5th leading cause of childhood mortality with an estimated one million deaths annually in children under five years of age. It is the single most common cause of bacterial meningitis beyond the newborn period in all age groups. By the end of 2009, 44 countries worldwide had introduced conjugate pneumococcal vaccine representing approximately 11% of the global birth cohort.

The prevention of invasive pneumococcal infection in developing areas of the world has been identified as a priority of the Bill and Melinda Gates Foundation. Working with the Global Alliance for Vaccines and Immunizations (GAVI), a collaborative effort between the World Health Organization (WHO), UNICEF, the U.S. Center for Disease Control and Prevention, and the World Bank, the Bill and Melinda Gates Foundation and other civil organizations have initiated a long term strategy to bring conjugate pneumococcal vaccine to eligible countries. Through the efforts and resources of GAVI, conjugate pneumococcal 13-valent vaccines have recently been introduced in Kenya, Sierra Leone, Yemen, Guyana, Honduras and Nicaragua. A dozen more countries will be included in the effort by the end of 2011, and 40 GAVI eligible countries will have infant and childhood pneumococcal vaccination programs by the end of 2015. Data to track the impact of such vaccine programs on childhood morbidity and mortality will be collected and shared with all stakeholders to ensure that the programs develop sustainability over time. Reminiscent of programs such as the polio vaccination partnership with the March of Dimes in the 1940s, this ambitious initiative will save lives and bring education regarding the value of immunizations to areas of the world that need them most.

2.3 Meningococcal vaccines

N. meningitidis is a gram-negative diplococcus that is commonly carried in the human nasopharynx. The specific risk factors that lead to invasive disease are incompletely defined. When an individual acquires the organism from another person, the most common outcome is colonization for a period of time. Some individuals can carry N. meningitidis in their upper respiratory tract for prolonged periods of time. Presumably, such individuals develop mucosal immune responses, including secretory immunoglobulin A that prevents invasion. Specific risk factors for the development of invasive disease include new acquisition of a new serotype, recent or current upper respiratory tract infection, smoking, alcohol consumption, and age.

When N. meningitidis invades, it enters the bloodstream, causing septicemia. Meningococcemia is classically associated with a petechial rash that rapidly progresses to purpura. It the most violent form of infection, referred to as purpura fulminans, death can ensue within a few hours. Bacteria seed the meninges in approximately half of all cases. Less commonly, patients develop lobar pneumonia, epiglottitis, septic arthritis, or purulent pericarditis. Meningitis accounts for nearly half of all invasive meningococcal infections; more than half of survivors have long-term complications including cognitive defects, cranial nerve palsies, and sensorineural hearing loss.

The 12 serogroups of N. meningitidis known to infect humans are characterized by the polysaccharide expressed on their capsule: A, B, C, 29-E, H, I, K, L, W-135, X, Y and Z. Clinically, the most relevant, and most prevalent types are A, B, C, W135, and Y. While uncommon, outbreaks caused by other capsular types have been described. Nasopharyngeal carriage of the bacterium is relatively common. In the U.S., carrier prevalence in the general population is approximately 10%. During the teen years, carriage has been described to be as high as 35%, and in environments of close contact such as military barracks and college residence halls, carriage rates may approach 100% (vanDeuren et al., 2000). The balance between carriage and the development of infection is influenced by both host and environmental factors (Caugant et al., 2007; Dull et al., 2001). Social factors also increase risk, such as intimate contact with an infected person, or living or working under crowded conditions, smoking, and alcohol consumption (MacLennan et al., 2006; Imrey et al. 1995).

The proportion of cases of meningococcal disease caused by individual serogroups A, B, C, W-135, and Y vary by geographic region. In developed countries, serogroup distribution also differs within regions. In Great Britain, for example, serogroups B and C account for over 90% of cases, while in New Zealand, serogroup B alone causes 87% of all cases. In contrast, meningococcal meningitis diagnosed in the African "meningitis belt," is usually caused by serogroup A. Attack rates during epidemics in Africa approach 1% of the population (Pinner et al., Moore P.s., 1992; Moore et al., 1989). In Saudi Arabia, where serogroup W-135 predominates, attack rates have been described at 25 per 100,000 population during the Hajj (Rosenstein et al., 2001; Pollard AJ, 2004; Wilder-Smith et al., 2003; Wilder-Smith et al., 2003). The country of Niger has recently experienced the emergence of serogroup X where it caused half of 1,139 cases in 2006 (Boisier et al., 20007).

In the U.S. between 1200 and 3500 cases of meningococcal disease occur annually (0.9 to 1.5 cases per 100,000 population). Data for 2006 through 2008 show that serogroups B, Y and C account for most of the U.S. cases (http://www.cdc.gov/abcs/reports-findings/survreports/mening09.html). Unlike the African 'meningitis belt', and areas of Asia where meningococcus type A infections are endemic, disease caused by serogroup A has not been detected in the U.S. since the late 1970s. Serotyping of 843 strains isolated between 1964 and 1967 demonstrated that serogroup A accounted for 1.3% of infections during that time period (Evans et al., 1968). An outbreak among skid row occupants occurred between 1975 and 1977 (Centers for Disease Control and Prevention 2009). Since that time, there has been a shift in serogroup predominance. Based on serotyping of 261 isolates from patients with meningococcal disease between 1989 and 1991, serogroups B and C accounted for more than 90% of cases. Furthermore, between 1998 and 2000, the proportion of serogroup Y cases increased from 2% to 33% of the total. Data for 2006

through 2008 show that serogroups Y (33%) and C (29%) continue to account for a large proportion of U.S. cases.

Given the fulminant nature of the infection, with an overall mortality rate of ~10%, prevention has become a priority. Vaccines for the prevention of invasive meningococcal infection were first available in the United States in 1971, but for more than two decades targeted only higher risk individuals. The first available vaccine, a polysaccharide capsular type C vaccine, was used almost exclusively in military recruits to control outbreaks that were being seen in military barracks. The high attack rate of meningococcal infection in this cohort of individuals is not surprising. Otherwise young, healthy individuals from different geographical areas of the country, where different N. meningitidis serotypes are prevalent, are brought together in close proximity under stressful conditions. Acquisition of a new serotype is common under such condition, and invasive disease more likely during physiologic stress and other behavioral risk factors.

A quadrivalent, non-conjugated pure polysaccharide meningococcal vaccine containing serotypes A, C, Y and W135 (Menomune) became available for use in the U.S. in 1981, and was primarily used to protect military recruits, travelers going to endemic areas and immunocompromised individuals. By 1999, the U.S. Centers for Disease Control and Prevention (CDC) and American College Health Association (ACHA) recommended the vaccine for all incoming college freshmen given the increased risk of invasive disease described in this population. As with other pure polysaccharide vaccines, protective immunity is short-lived, but given the brief period of increased risk in college freshman and in military recruits, the vaccine was widely used. As with pure polysaccharide HIB and pneumococcal vaccines, lack of T-cell engagement leads to inability to boost prior responses. Similarly, no change in nasopharyngeal carriage was expected. Subsequent vaccine development allowed for emerging conjugate vaccines, and led to changes in how these vaccines are used currently.

Globally, the first large scale experience with conjugate meningococcal vaccines occurred in the 1990s. One of the best examples comes from the United Kingdom where an epidemic of group C meningoccocal infection was causing a serious public health problem. The epidemic peaked in 1999 with an estimated 1500 cases and 150 deaths in that country alone. In November 1999, the public health ministry introduced a monovalent group C meningococcal vaccine as a public health measure, focusing first on vaccinating teenagers. Population based surveillance was used to monitor the incidence of disease as the vaccination program was introduced. Within 12 months of vaccine delivery through public health efforts, a marked decline in the incidence of disease was observed, and the vaccine program was expanded to young children. Vaccine effectiveness was estimated to be 90% for vaccinated individuals, but a broader scale benefit was noted for the overall population, argued to be secondary to a reduction in nasopharyngeal carriage of the organism leading to reductions in disease transmission among the unvaccinated population as well. The observation that conjugate vaccines lead to reductions in nasopharyngeal carriage and provide a community immunity benefit that extends to those who are not vaccinated is unique to conjugate vaccines as pure polysaccharide formulations do not afford this benefit. In addition to the monovalent conjugate group C vaccine used to control the U.K. epidemic, several other mono and bivalent conjugate vaccines are currently available in the global market.

The first conjugate meningococcal vaccine (which includes immunogens targeting the same four serotypes in the polysaccharide vaccine Menomune-- A, C, Y and W135) became available in the U.S. in 2005, it was immediately recommended that it replace polysaccharide vaccine for most individuals. Since clinical vaccine trials demonstrated safety and efficacy up to age 55, but not beyond, the polysaccharide vaccine is still officially recommended for individuals 55 years and older. Conjugate meningococcal vaccines are recommended for use in high risk individuals including those with terminal complement deficiency, asplenia, HIV infection, and in those who travel to areas of the world endemic for meningococcal infection. In addition, given the epidemiology of invasive meningococcal infection during adolescence, conjugate meningococcal vaccine was added to the universal immunization schedule starting at 11-12 years of age in 2005. Because of concerns that vaccine effectiveness may drift over time, the U.S. Advisory Committee on Immunization Practices added a second dose recommendation at age 16 years (up to age 21) as a booster.

Recent clinical trials have also evaluated the conjugate vaccines for safety and efficacy in younger children, and by 2011, vaccine became available for use as early as 9 mos of age for high-risk individuals and travelers (Menactra). A combination HIB-Meningococcal C/Y vaccine that was studied in clinical trials in the U.S. is currently under review for licensure by the Food and Drug Administration. In the U.S., the ACIP has been reluctant to recommend universal use of meningococcal conjugate vaccines under the age of 11 years, since more than half of infant infections are currently caused by the non-vaccine serotype B meningococcus. Meningococcal vaccines designed to protect individuals against serogroup B illness are in phase 3 clinical vaccine efficacy trials.

2.3.1 Meningococcus serotype B and the unique challenges it presents

Given the epidemiology of invasive meningococcal disease, including a substantial contribution from N. meningitidis type B should not be capitalized, it is logical to question why it has been so difficult to develop a serotype B vaccine. The native group B polysaccharide is a poor vaccine candidate because it contains epitopes that cross-react with sialylated proteins in human brain. New strategies have emerged to use alternative components of the group B meningococcus as vaccine antigens since such residues have been identified that are not cross reacting with the same human tissues. Ultimately, the development of a safe and effective B vaccine will likely capitalize on these non-cross reacting group B antigens from genetically modified strains. Several such vaccine candidates are already undergoing clinical trials.

Reported cases of meningococcal meningitis in the U.S. are currently at historically low rates. It is premature to credit the introduction and implementation of conjugate meningococcal vaccines for this epidemiologic observation, but in the coming years it will become clear whether this promising trend continues. The obvious decline in both HIB and pneumococcal meningitis following the introduction of vaccines for those infections is already compelling. Vaccine programs are highly effective. A summary of the current Advisory Committee on Immunization Practices for use of HIB, pneumococcal and meningococcal vaccines in summarized in **Table 2.**

Vaccine	Age Given	Recommendation	High Risk Conditions
HIB conjugate	2, 4, 6, 12-15 mos*	Universal	Universal
Pneumococcal polysaccharide	After 23 mos	Following conjugate series, 2 doses 5 yrs apart	Sickle cell disease, asplenia, inherited or acquired immune deficiency, chronic cardiac and/or pulmonary disease, CSF leaks, renal insufficiency, diabetes
Pneumococcal conjugate	2, 4, 6, 12-15 mos	Universal	Universal
Meningococcal polysaccharide	56 yrs and older	High risk	See risk factors in conjugate box below. Meningococcal conjugate vaccine not approved for use after age 55 yrs.
Meningococcal conjugate	11-21 yrs 9 mos-55 yrs	Universal High Risk	Universal Terminal complement or properdin deficiency, asplenia, military recruits, college freshman living in catered halls, HIV infection, travel to endemic areas of the world

*6 mos dose not needed if PedvaxHIB is used

Table 2. Summary of recommendations from the Advisory Committee on Immunization Practices (ACIP) of the United States for the use of HIB, pneumococcal and meningococcal vaccines

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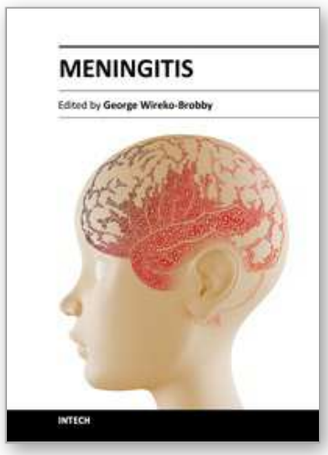

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Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

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