Meningococcal disease: changes in epidemiology and prevention

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Abstract: The human bacterial pathogen Neisseria meningitidis remains a serious worldwide health threat, but progress is being made toward the control of meningococcal infections. This review summarizes current knowledge of the global epidemiology and the pathophysiology of meningococcal disease, as well as recent advances in prevention by new vaccines. Meningococcal disease patterns and incidence can vary dramatically, both geographically and over time in populations, influenced by differences in invasive meningococcal capsular serogroups and specific genotypes designated as ST clonal complexes. Serogroup A (ST-5, ST-7), B (ST-41/44, ST-32, ST-18, ST-269, ST-8, ST-35), C (ST-11), Y (ST-23, ST-167), W-135 (ST-11) and X (ST-181) meningococci currently cause almost all invasive disease. Serogroups B, C, and Y are responsible for the majority of cases in Europe, the Americas, and Oceania; serogroup A has been associated with the highest incidence (up to 1000 per 100,000 cases) and large outbreaks of meningococcal disease in sub-Saharan Africa and previously Asia; and serogroups W-135 and X have emerged to cause major disease outbreaks in sub-Saharan Africa. Significant declines in meningococcal disease have occurred in the last decade in many developed countries. In part, the decline is related to the introduction of new meningococcal vaccines. Serogroup C polysaccharide-protein conjugate vaccines were introduced over a decade ago, first in the UK in a mass vaccination campaign, and are now widely used; multivalent meningococcal conjugate vaccines containing serogroups A, C, W-135, and/or Y were first used for adolescents in the US in 2005 and have now expanded indications for infants and young children, and a new serogroup A conjugate vaccine has recently been introduced in sub-Saharan Africa. The effectiveness of these conjugate vaccines has been enhanced by the prevention of person-to-person transmission and herd immunity. In addition, progress has been made in serogroup B-specific vaccines based on conserved proteins and outer membrane vesicles. However, continued global surveillance is essential in understanding and predicting the dynamic changes in the epidemiology and biological basis of meningococcal disease and to influence the recommendations for current and future vaccines or other prevention strategies.

Keywords: Neisseria meningitidis, meningococcal disease, conjugate vaccines, meningococcal vaccines

Introduction

Human infections caused by meningococcus (Neisseria meningitidis) remain a serious health problem, infecting 500,000 to 1.2 million people and killing between 50,000 and 135,000 per year worldwide.1 Infections due to N. meningitidis can present as a spectrum of clinical illness, with meningitis and septicemia being the most common, but also including pneumonia, septic arthritis, pericarditis, conjunctivitis, and urethritis.2 Meningococcal meningitis (infection of the subarachnoid space.
involving the meninges and the central nervous system) often presents with fever, rash, meningeal signs (headache, stiff neck), and altered mental status. Deafness or other cranial nerve loss and long-term cognitive disability can also be a consequence. Meningococcal septicemia is a fulminant infection (sometimes < 24 hours) with initial symptoms that are nonspecific (fever, muscle aches) and is difficult to diagnose before the onset of a maculopapular, petechial, or purpuric rash. Septicemia can result in rapid onset of hypotension, multiorgan dysfunction shock, peripheral ischemia, limb loss, and death. Overall mortality for invasive meningococcal disease is approximately 10% of infected individuals, but is up to 40% in cases of septicemia.

The diagnosis of meningococcal meningitis is confirmed by cerebrospinal fluid pleocytosis, Gram stain, polymerase chain reaction, culture of cerebrospinal fluid, or cultures of blood or skin lesions. Diagnosis of other invasive meningococcal disease is based on blood or skin lesion culture or Gram stain, polymerase chain reaction, and culture of normally sterile sites, such as synovial or pericardial fluid. In addition to polymerase chain reaction, rapid tests used to identify *N. meningitidis* based on latex agglutination or chromatography immunodetection have been used. Early antibiotic treatment with a third-generation cephalosporin, penicillin, or meropenem to stop proliferation of *N. meningitidis* immediately is the primary goal of treating infected individuals. Due to the potential for contact and epidemic spread, rapid onset, high case-fatality rate, and neurologic sequelae of meningococcal disease, a single case elicits an immediate public health response. Chemoprophylaxis with rifampin, ciprofloxacin, ceftriaxone, or azithromycin to eradicate nasopharyngeal carriage of the meningococcus is recommended for close contacts of patients to protect susceptible individuals and prevent further transmission. Current prevention measures also include immunization with meningococcal polysaccharide conjugate vaccines directed at one to four meningococcal serogroups, ie, A, C, Y, and W-135. Serogroup B vaccines based on outer membrane vesicles have been used to control serogroup B outbreaks.

**Changing global epidemiology**

Meningococci are classified according to serologic typing based on the biochemical composition of the capsular polysaccharide. In total, 13 serogroups of *N. meningitidis* have been reported, with A, B, C, E, H, I/K, L, W-135, X, Y, and Z confirmed genetically. However, six serogroups (A, B, C, W-135, X, and Y) cause almost all worldwide life-threatening disease. Genomic typing (eg, multilocus sequence typing) and whole genome comparisons have unlocked a broader understanding of the global epidemiology of meningococcal disease. With multilocus sequence typing, meningococcal isolates are classified into different sequence types based on polymorphisms in seven housekeeping genes considered not to be under selective pressure.

The incidence of meningococcal disease is cyclical in nature, having peaks and troughs every 5–8 years in some epidemiologic settings. However, disease patterns and incidence vary in populations geographically and over time among the different invasive meningococcal serogroups and sequence type (ST) clonal complexes.

In the US, active bacterial core surveillance is a prospective laboratory and population-based surveillance system that tracks invasive bacterial pathogens including *N. meningitidis* (Figure 1). The incidence of meningococcal disease in the US in the last quarter century peaked at roughly 1.7 per 100,000 in the mid 1990s and since has continually declined to 0.35 per 100,000 in 2007. The distribution of serogroups causing disease has also shifted. Serogroup C accounted for the majority of cases in the first decade of surveillance. However, the incidence of serogroup C diminished significantly after 1999, before the introduction of meningococcal conjugate vaccines. In comparison, the rates of serogroup B was consistent between 1992 and 2001, but have also declined since 2001. Serogroup Y cases emerged in the mid 1990s and the disease incidence peaked in 1997. Although decreases in serogroup Y incidence have occurred since 2001 with the overall decline in the incidence of meningococcal disease, serogroup Y continues to cause disease in the population (Figure 1). Almost all of the serogroup C and Y meningococcal disease was caused by the ST-11 complex and ST-23 clonal complexes, respectively, suggesting that closely related strains circulate in the community and cause sporadic disease.

Serogroup A is associated with the highest incidences of meningococcal disease. In sub-Saharan countries of Africa, extending from Senegal in the west to Ethiopia in the east, known as the African meningitis belt, there have been large periodic epidemics of serogroup A meningococcal disease occurring every 8–10 years since 1905, with rates of disease that can exceed 1000 cases per 100,000. In the last two decades, two ST clonal complexes, ST-5 and ST-7, have been responsible for African meningitis belt outbreaks due to serogroup A. The patterns in the region are linked to environmental factors, such as climatic changes (dry season, winds of the Harmattan), coinfection, crowding, and specific population susceptibility.
In the US as well as other industrialized countries, outbreaks of serogroup A disease occurred with similar periodicity during the first part of the 20th century, but disappeared after World War II for unknown reasons. Even though it is now virtually nonexistent in the US and most developed countries, serogroup A meningococcal disease remains a public health threat in sub-Saharan Africa and other areas of the developing world. Over the last two decades, great strides have been made in development of meningococcal conjugate vaccines with the recent successful introduction of a new serogroup A meningococcal conjugate vaccine, MenAfriVac™ (Serum Institute of India Ltd., Pune, India), in sub-Saharan Africa (see “New vaccines for prevention” section).

Serogroup B meningococcal disease is generally associated with a lower incidence of disease compared with serogroups A and C. However, serogroup B is an important cause of sporadic disease and of prolonged outbreaks in developed countries. In the US, the incidence of serogroup B meningococcal disease has fluctuated, but currently is contributing to 30%–40% of all meningococcal disease. In the Pacific Northwest (Oregon and parts of Washington State), serogroup B (clonal complex ST-32) caused a prolonged outbreak in 1993–2007. Curiously, serogroup B disease is now rare in sub-Saharan Africa. There is greater genetic diversity and thus antigenic diversity in serogroup B strains that cause sporadic serogroup B disease compared with other serogroups, with ST-41/44, 

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**Figure 1 (A)** Active bacterial core surveillance of the incidence of meningococcal disease by serogroups, 1988–2010, Metropolitan Atlanta, GA. (B) Cases with unknown serogroups have been shown to be genetically serogroups B, C, and Y, and thus were imputed by proportionally categorizing into those serogroups.
ST-32, ST-18, ST-269, ST-35, and ST-8 causing the majority of serogroup B cases, and a number of other STs are found in collections of serogroup B isolates. Novel serogroup B strains are occurring worldwide and the diversity of clonal complexes causing serogroup B presents a challenge to control through vaccination. Also, a number of ST-11 isolates, a clonal complex usually associated with serogroup C, express the serogroup B capsule. As described below, meningococcal “capsule-switching” due to transformation and recombination at the cps locus allows escape of vaccine-induced or natural protective immunity. This escape mechanism has raised concerns about serogroup replacement as a threat to the effectiveness of meningococcal conjugate vaccines. Serogroup B strains are of special concern due to the absence of a vaccine for the routine prevention of serogroup B disease. The serogroup B capsule is poorly immunogenic due to identity with human antigens and is not a component of meningococcal conjugate vaccines. However, outer membrane vesicles have been developed for control of serogroup B clonal outbreaks. An outer membrane vesicle vaccine helped control a serogroup B outbreak in New Zealand in 2004 and a serogroup B outer membrane protein-containing vaccine, VA-MenGOC-BC® (Finlay Institute, Habana, Cuba), has been extensively used (over 55 million doses) in Cuba and Latin America. New approaches based on conserved proteins are in late-stage clinical trials.

The other serogroup that accounts for a majority of meningococcal disease cases throughout the world is serogroup C. In the US, serogroup C disease is responsible partly for endemic disease as well as clusters of local outbreaks, accounting for approximately 30% of overall disease. Increases in serogroup C meningococcal disease were seen in the 1980s and 1990s worldwide, attributed to the spread of a hypervirulent ST-11 complex/ET-37 complex clone. The meningococcal serogroup C conjugate vaccine was first introduced in the UK in 1999 to address the growing incidence of disease. The incidence of meningococcal disease decreased by one half from 1999 to 2006 in Europe (following the introduction of serogroup C conjugate vaccines), but has subsequently stabilized. As noted above, since the turn of this century, there has been a significant decline in overall meningococcal disease as well as serogroup C disease in the US.

With periodic exceptions, other serogroups account for less than 10% of all meningococcal disease. As noted, in parts of the US, serogroup Y emerged in the early 1990s and increased in incidence until the mid to late 1990s. Serogroup Y increased to almost 50% of cases in the mid 1990s, but accounted only for 2% of all meningococcal infections in the early 1990s. In 1998, a carriage study examining nasopharyngeal specimens from 1818 high school students from hypersporadic counties in the metropolitan area of Atlanta, GA, found the rate of carriage to be 7.7% and of these, 48% were serogroup Y. However, in 2006–2007, a similar carriage study in high school students found a much lower proportion of serogroup Y carriage. The lower frequency of serogroup Y and overall meningococcal carriage was reflected in a decrease in invasive meningococcal cases between 1998 and 2007. Serogroup Y disease has also been reported in South America, South Africa, Europe, and Israel. Most of the serogroup Y disease increase is associated with ST-23 and ST-167 clonal complexes. Serogroup X (ST-181) has caused localized outbreaks in certain African countries, including Kenya, Niger, and Ghana, but is rarely seen as a cause of disease outside of Africa. Serogroup W-135 has emerged in the last two decades as a cause of epidemic outbreaks in Hajj pilgrimages and in the African meningitis belt. Outbreaks caused by the spread of W-135 (ST-11) strains closely related to ST-11 serogroup C strains are believed to be in part attributable to capsule switching.

Pathophysiology and natural history

N. meningitidis, a Gram-negative β-proteobacterium of the family Neisseriaceae, is an exclusive pathogen in humans, carried asymptomatically in the nasopharynx by 5%–10% of adults in nonepidemic periods. It is an aerobic diplococcus and can be either structurally encapsulated or not encapsulated. Capsule polysaccharide expression of the bacteria plays a key role in meningococcal pathogenesis. N. meningitidis strains that cause invasive disease are almost always encapsulated, which helps survival of the bacteria during invasive disease and promotes transmission as well as protection from antibodies and phagocytic cells. With the exception of the serogroup A and X capsules, meningococcal capsular polysaccharides associated with invasive disease are composed of or contain sialic acid units. Serogroups B and C are (α2→8)-linked and (α2→9)-linked polysialic acid, respectively, while serogroups Y and W-135 are alternating units of D-glucose or D-galactose and sialic acid, respectively. The serogroup A capsule is composed of (α1→6)-linked N-acetyl-mannosamine-1-phosphate, while serogroup X expresses (α1→4)-linked N-acetyl-D-glucosamine 1-phosphate. Other properties of the meningococcus that contribute to its virulence are expression of surface adhesive proteins such as pili that
allow movement (twitching motility) and binding to and passage into epithelial cells, meningococcal endotoxin or lipo-oligosaccharide that binds to TLR-4 and produces acute vascular and cerebrospinal fluid inflammation, and proteins that bind iron as an important growth factor during colonization.1

*N. meningitidis* has a dynamic biology in that it undergoes frequent (up to 10^3 cell) antigenic variability and escape from vaccine-induced or natural protective immunity.2,3 Genetic mechanisms of variability include horizontal gene transfer of DNA sequences,4 phase variation through a slipped strand mispairing mechanism,5–7 and transposition of mobile elements8 that create surface structure variability of the organism, gene conversion, and antigenic variation via homologous recombination9–12 and regulation by the two-component regulatory system.13 Capsular switching occurs through horizontal gene transfer, allowing the bacteria to exchange serogroup specific capsule biosynthesis genes and thus change its capsular phenotype.14,15,18 This mechanism is detected by identifying strains that are genetically related, such as by multilocus sequence typing. Capsular switching is a potential concern for vaccines that do not include protection against all meningococcal serogroups. However, no meaningful increase in meningococcal disease due to other serogroups occurred after the introduction of serogroup C conjugate vaccines in the UK.16

Understanding meningococcal carriage and human-to-human transmission is a key to the understanding of meningococcal epidemiology. Hosted only by humans, transmission of the meningococcus occurs usually through large respiratory droplets from asymptomatic human carriers or individuals who are ill with upper respiratory symptoms. Meningococcal disease occurs usually 1–10 days after acquisition. Asymptomatic nasopharyngeal carriage can be another outcome of transmission and acquisition. Carriage can last for days to several months and is found in 3%–25% of human populations in cross-sectional studies.18 Why the meningococcus causes invasive disease in a few individuals while colonizing the nasopharynx of many has been a fundamental question in meningococcal biology and pathogenesis. The absence of protective humoral bactericidal antibodies is a major host risk factor of invasive meningococcal disease.19 Infants and very young children are at highest risk of developing meningococcal disease before serum bactericidal antibodies develop and after maternal antibodies have waned. Additional factors for abnormal bactericidal activity in human sera include congenital or acquired immunoglobulin deficiencies and complement deficiencies.20–26

Other individual risk factors for meningococcal disease that have been found are active and passive smoking,27–29 concurrent respiratory infections,30–32 and crowding.33–36 The transmission of the meningococcus is clearly elevated in close contact37–39 and crowded living conditions (eg, barracks, dorms, pilgrimages).37–39 While the majority of invasive meningococcal cases are sporadic, a total of 69 outbreaks were identified in the US between mid 1994 and mid 2002, most of which were serogroup C outbreaks occurring in both the community and in institutional settings, such as nursing homes, schools, and colleges.40 In addition, climatic conditions change the risk of invasive meningococcal disease. While meningococcal disease occurs year round, the majority of cases occur during the winter and early spring.41 In the meningitis belt in sub-Saharan Africa, epidemics usually occur in the dry season between March and April when it is hot, arid, and dusty, and last until the rainy season.42,43

**New vaccines for prevention**

An ideal vaccine for prevention of meningococcal disease would be effective against the invasive serogroups of meningococci and would elicit long-lasting immunity in all age groups, especially infants, children, and adolescents. Meningococcal polysaccharide vaccines for A, C, Y, and W-135 have been available since the 1970s and 1980s. However, they have been or are being replaced in routine use by polysaccharide-protein conjugate vaccines. Meningococcal polysaccharides alone elicit a poor immunologic response in infants and toddlers and the serum antibody response is generally short-lived, and even in older children and adults the protective response lasts approximately 5 years. In addition, the serogroup C and A polysaccharide vaccines have been shown to induce a hyporesponsive state to repeated meningococcal C or A polysaccharide administration.44

The immunogenicity of the meningococcal polysaccharide (shift from a T-independent to a T-dependent immune response) can be greatly improved by conjugation with a protein carrier (diphtheria or tetanus toxoid). Meningococcal serogroup C conjugate vaccines were first introduced in 1999 in the UK. They produced a dramatic decrease in the number of deaths and cases of invasive serogroup C meningococcal disease, as well as a 66% reduction in the carriage of *N. meningitidis*.45 The remarkable herd immunity effect of these conjugate vaccines through preventing acquisition and transmission accounts for about 50% of their effectiveness.46–48 Following the success of the meningococcal group C conjugate vaccine in circumventing the problems of the plain polysaccharide vaccine in the UK,49 tetravalent conjugate vaccines
incorporating capsular groups A, C, Y, and W-135, and recently a bivalent C, Y conjugate, covalently linked to tetanus or diphtheria toxoid, have been developed and are in clinical use.\textsuperscript{93} In May 2005, the US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommended the first quadrivalent meningococcal conjugate vaccine for routine use in all US adolescents for protection against serogroups A, C, W-135, and Y.\textsuperscript{5} While the first quadrivalent conjugate vaccines were shown to have very high efficiency at generating protective bactericidal antibody titers, the overall population impact of the vaccine in the US was difficult to determine due to the falling incidence of disease and the initial low vaccine uptake.\textsuperscript{94} Other tetravalent and bivalent meningococcal conjugate vaccines are now licensed\textsuperscript{95} and the current age range of licensure approval is 2–55 years, with licensure for young children and infants approved by the US Food and Drug Administration for the C, Y, \textit{Haemophilus influenzae} type b conjugate.

Even though the generalized use of the quadrivalent conjugate vaccine would be ideal, the cost of the vaccine has made these vaccines unaffordable for routine use in developing countries. The Meningitis Vaccine Project, a partnership between the World Health Organization and the Program for Appropriate Technology in Health, aims to eliminate epidemics of invasive meningococcal disease in sub-Saharan Africa and has developed a serogroup A-specific vaccine at an affordable price ($<50 \text{ cents per dose}).\textsuperscript{96,97} The vaccine, named MenAfriVac, was prequalified by the World Health Organization in June 2010.\textsuperscript{98} Mass vaccination campaigns began in December 2010 in Burkina Faso and are underway in other parts of the meningitis belt.\textsuperscript{98,99} This is an important public health priority to reduce the incidence of serogroup A meningococcal disease in this region, which has been so devastated by epidemics due to this serogroup.

Serogroup B polysaccharide of \textit{N. meningitidis} is not included in the quadrivalent meningococcal conjugate vaccines due to the structural homology between the capsular polysaccharide and human antigens, including the human neural cell adhesion molecule.\textsuperscript{22,100} Efforts to develop a serogroup B-specific vaccine have used outer membrane vesicles and/or targeted relatively conserved and antigenic meningococcal outer membrane proteins. Progress is being made in the development of these vaccines.\textsuperscript{101}

\section*{Conclusion}

The human bacterial pathogen \textit{Neisseria meningitidis} remains a serious worldwide health threat, but progress is being made toward the control of meningococcal infections. The incidence of meningococcal disease has decreased in developed countries in the last decade due at least in part to the new meningococcal polysaccharide-protein conjugate vaccines’ effect against serogroups C, Y, W-135; and a serogroup A meningococcal conjugate vaccine is now being introduced into sub-Saharan Africa, a region with the highest rates of meningococcal disease. However, meningococcal disease is characterized by fluctuations in incidence and shifts in serogroups and genotypes. The basis for the dynamic epidemiology of meningococcal disease is not completely understood. Continued surveillance is essential in detecting, understanding, and predicting the changes in the epidemiology of meningococcal disease. Active surveillance for serogroup-specific and genotype-specific invasive disease allows for close monitoring of trends in meningococcal disease over time. A detailed understanding of meningococcal disease in communities will affect recommendations for current or future vaccines or other prevention strategies. Meningococcal vaccines that are effective and affordable against invasive strains, elicit long-lasting immunity in all age groups, and provide significant herd immunity will allow the development of strategies for the global elimination of meningococcal disease.

\section*{Disclosure}

The authors report no conflicts of interest in this work.

\section*{References}


