Epidemiological Profile of Meningococcal Disease in the United States

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*Neisseria meningitidis* is a leading cause of bacterial meningitis and other serious infections worldwide. The epidemiological profile of *N. meningitidis* is highly changeable, with great differences in disease incidence and serogroup distribution. Six serogroups (namely serogroups A, B, C, W-135, X, and Y) are responsible for most cases of meningococcal disease worldwide; the epidemiological profile of disease caused by each serogroup is unique. No vaccine is available for endemic disease caused by serogroup B strains. Two tetravalent (A/C/Y/W-135) meningococcal vaccines are licensed in the United States: a purified polysaccharide product and a polysaccharide-protein conjugate vaccine. The conjugate vaccine is recommended for all adolescents, although vaccine coverage remains low, and other groups at high risk of infection. A comprehensive program to prevent invasive meningococcal disease in the United States will require vaccination of infants; several conjugate vaccines for infants may become available in the near future. Broadly protective vaccines for endemic serogroup B disease are also needed.

*Neisseria meningitidis* remains a major cause of bacterial meningitis and other invasive bacterial infections worldwide [1–4]. A remarkable characteristic of meningococcal epidemiology is that it is highly fluid, with major fluctuations in the incidence of endemic disease and the occurrence of outbreaks and epidemics. In addition, meningococcal serogroup distribution is highly regional and cyclical.

The purpose of this review is to discuss the current epidemiological profile of meningococcal disease and the vaccines that are presently available in the United States. Recent experiences with meningococcal vaccines in the United Kingdom and New Zealand will also be reviewed, because they illustrate the potential public health impact of meningococcal conjugate and outer membrane protein–based serogroup B vaccines, respectively.

**MENINGOCOCCAL SEROGROUPS**

Virulent *N. meningitidis* strains have a polysaccharide capsule, which allows the organism to cause invasive diseases, such as bacteremia and meningitis. Unencapsulated strains, which are frequently found in the pharynx of asymptomatic carriers, have only rarely been determined to cause invasive infections [5, 6]. Of the 13 different polysaccharide capsular types, only 6 frequently cause disease globally (A, B, C, W-135, X, and Y), although substantial rates of serogroup X disease are restricted to parts of sub-Saharan Africa [1].

Serogroup A *N. meningitidis* occurs primarily in the "meningitis belt" of sub-Saharan Africa and has been responsible for the largest and most devastating meningococcal epidemics [7, 8]. Serogroup A meningococcal disease also occurs in other parts of the world, such as China and Russia, but is currently extremely rare in the United States, despite the documented introduction of virulent serogroup A strains in this country [9]. Serogroup B strains cause a substantial proportion of meningococcal disease endemic in many...
parts of the world, including the United States, as well as pro-
longed epidemics [10, 11]. Serogroup C, which is also a promi-
ent serogroup in many regions of the world, has occasionally
caused epidemics and frequently causes outbreaks [12]. Sero-
group Y strains cause a high proportion of cases in the United
States and other countries in the Americas [13, 14]. Although
not generally considered to be one of the major meningococcal
serogroups, serogroup X strains have been reported to cause a
substantial amount of meningococcal disease in some countries
in Africa, such as Niger, Togo, and western Kenya [15–17]. The
reasons for the distinct serogroup distribution in different
regions of the world are unknown, but possible mechanisms
include differences in population immunity and environmental
factors. A summary of the global distribution of meningococcal
serogroups is shown in Figure 1.

MOLECULAR MECHANISMS THAT PLAY A
ROLE IN THE DYNAMIC EPIDEMIOLOGICAL
PROFILE OF MENINGOCOCCAL DISEASE

Several mechanisms are used to change the characteristics (eg,
antigenic structure or resistance to antibiotics) of meningoc-
coccus. Many of these changes occur through horizontal gene
transfer, which permits the organism to obtain large DNA se-
quen ces from other meningococcal strains or other species [18].
N. meningitidis also uses multiple other mechanisms to achieve
antigenic variation [19–26]. One such mechanism is gene con-
version, which involves autologous recombination. For ex-
ample, PilE is a prominent component of the N. meningitidis
pilus that is encoded by pilE. Contiguous to pilE are 8 truncated
pseudogenes that are able to undergo recombination with pilE,
which allows for generation of major antigenic variability with-
out the acquisition of foreign DNA.

Capsular switching is a genetic mechanism that allows N.
meningitidis to change its capsular phenotype. Outbreaks of N.
meningitidis infection can be started or sustained using this
mechanism, which permits immunologic escape from immu-
nity to the original serogroup [27–30]. Capsular switching oc-
curs through horizontal gene transfer and is generally defined
as strains that belong to the same genetic lineage (as deter-
mained, for example, by multilocus sequence typing) but have
a different polysaccharide capsule. Capsular switching presum-
ably occurs when a person is cocolonized in the pharynx with
≥2 meningococcal strains [31, 32]. For example, the boyfriend
of a young girl who died of serogroup B meningococcal disease
had pharyngeal colonization with serogroup C strain that was
otherwise genetically indistinguishable [29]. A significant per-
centage of meningococcal strains that cause disease in the
United States apparently have arisen through the mechanism
of capsular switching [33].

Capsular switching appeared to be responsible for an out-
break of serogroup W-135 disease during the 2000 Hajj in Mecca,
Saudi Arabia. Subsequent to this outbreak, the epidemic
strain spread globally and caused an epidemic in Burkina Faso
[34, 35]. Capsular switching was also observed in the 1990s
during an outbreak of serogroup B disease in Oregon, with
some serogroup C strains found to be otherwise genetically
indistinguishable from the serogroup B outbreak strain [10,
27].

A key concern is that, with mass vaccination using vaccines
that do not include protection against all of the major menin-

Figure 1. Worldwide distribution of major meningococcal serogroups [1]. Reprinted from Vaccine 27(Suppl 2), Harrison LH, Trotter CL, Ramsay ME, Global Epidemiology of Meningococcal Disease, B51–B63, Copyright 2009, with permission from Elsevier.
Meningococcal Disease in the United States

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Figure 2. Mean annual incidence of invasive meningococcal disease, 1997–2007, by age group [39].

gococcal serogroups, there could be an increase in the incidence of meningococcal disease caused by strains not included in the vaccine. This could occur through the mechanisms of capsular switching or capsular replacement. Serotype replacement has been observed since the routine use of pediatric pneumococcal conjugate vaccine began in the United States in 2000 [36, 37]. However, meningococcal serogroup replacement has not been observed in the United Kingdom since the introduction of routine vaccination with serogroup C conjugate vaccines [38]. Serogroup C carriage is relatively uncommon, even in the face of a substantial incidence of serogroup C meningococcal disease; it remains to be seen whether serogroup replacement will occur with the use of meningococcal vaccines that cover a higher proportion of carriage strains.

Increases in the incidence of meningococcal disease have also been associated with changes in noncapsular outer membrane proteins. This observation has implications for outer-membrane protein–based vaccines for the prevention of serogroup B meningococcal disease. In Maryland, an increase in the incidence of serogroup C and serogroup Y meningococcal disease occurred in association with a substantial antigenic shift in several outer membrane proteins [14]. For serogroup C, horizontal gene transfer led to major antigenic changes in FetA, and the porA gene was entirely deleted from some strains. For serogroup Y, major antigenic changes were caused by horizontal gene transfer involving 3 outer membrane protein genes.

RISK FACTORS

There are numerous known risk factors for meningococcal disease; incidence varies greatly by age, with infants having the highest risk of disease (Figure 2) [13]. A low level of serum bactericidal antibody is among the most important host factors associated with risk of infection [40, 41]. Low socioeconomic status and minority ethnicity have also been found to be associated with increased risk [4, 13, 42, 43]. Conditions associated with immune compromise, such as functional or anatomic asplenia, human immunodeficiency virus infection, and genetic polymorphisms and deficiencies in components of the innate immune system, have been associated with increased risk of meningococcal disease [44–52].

Environmental factors associated with the risk of both invasive disease and carriage include recent or concurrent upper respiratory infection, such as influenza [53–58]. In the meningitis belt of sub-Saharan Africa, epidemics commence during the dry season and end at the onset of the rainy season [59]. Population crowding has long been known to be associated with increased risk of meningococcal disease [60]. More recently, behavioral risk factors, such as passive and active smoking, pub and bar patronage, kissing, and living in a university dormitory, have been shown to be associated with risk of meningococcal carriage and disease in a variety of studies [61–71].

EPIDEMIOLOGY IN THE UNITED STATES

The Active Bacterial Core surveillance (ABCs) network, a population-based surveillance system for invasive meningococcal disease and other serious bacterial pathogens, has provided invaluable information about the epidemiological profile of meningococcal disease in the United States [72]. Because active surveillance methods are used, ABCs is highly sensitive for culture-positive N. meningitidis disease and infection caused by other bacterial pathogens. In 2009, ~40 million persons (~13% of the US population) lived in an area with ABCs for meningococcal disease.

Since World War II, the annual incidence of meningococcal disease has varied from 0.5 to 1.5 cases per 100,000 population. During the past 3 decades, the incidence has increased and decreased in multiyear cycles (Figure 3) [3, 73]. The most recent
Figure 3. Incidence of invasive meningococcal disease, by year, in the United States, 1976–2006 [73].

peak in incidence occurred during the mid-1990s. Subsequently, there was a decrease to ~0.35 cases per 100,000 population in 2007, caused by decreases in the 3 most common serogroups in the United States: B, C, and Y. Of interest, the current nadir in incidence began before the introduction of tetravalent meningococcal conjugate vaccine (MCV4) and has been more sustained than in previous years. In addition, MCV4 does not contain a serogroup B component and, therefore, had no influence on the reduction in the incidence of serogroup B disease. The factors responsible for this substantial decrease in the overall rate of meningococcal disease are unknown but could include population immunity to the strains currently circulating in the United States, changes in the prevalence of behavioral risk factors, and unknown variables.

Meningococcal serogroup distribution varies over time. For example, serogroup Y accounted for only 2% of meningococcal infections during 1989–1991 [42]. By the mid-1990s, the incidence of serogroup Y disease increased and serogroup Y strains accounted for one-third of meningococcal infections [13]. The increase in the incidence of serogroup Y disease in Maryland occurred primarily in children <15 years of age and in adults >25 years of age [74]. The incidence of serogroup C meningococcal disease also increased and subsequently decreased during the 1990s. Serogroup W-135 disease, which currently accounts for a small percentage of cases, was previously more common [13, 75, 76]. On the basis of ABCs data, the serogroup distribution in the United States in 2007 was serogroup B (25% of cases), serogroup C (30%), and serogroup Y (37%), with 9% of cases caused by serogroup W-135, other serogroups, and nongroupable strains [77]. The proportion of serogroup B isolates is higher in Oregon, as is the incidence of serogroup B disease, because of an ongoing outbreak involving a serogroup B sequence type–32 complex/enzyme type–5 complex clone [10].

As the incidence in meningococcal disease increased in the United States during the 1990s, the number of outbreaks of N. meningitidis infection also increased. From mid-1994 through mid-2002, 76 outbreaks in the community, specifically in colleges, primary and secondary schools, and nursing homes, were identified throughout the United States [12, 78–81]. The majority of the outbreaks were caused by serogroup C strains.

CURRENT MENINGOCOCCAL VACCINES IN THE UNITED STATES

Two tetravalent (A/C/Y/W-135) meningococcal vaccines are licensed in the United States; one of these is a purified polysaccharide product, and the other is a polysaccharide-protein conjugate vaccine (MCV4) with diphtheria toxoid as the protein carrier [82]. MCV4 was licensed in 2005 and is recommended for all US adolescents. In 2007, despite this universal recommendation, only 33% of persons aged 13 years had received MCV4, as determined by the National Immunization Survey [83]. MCV4 is also recommended for college freshmen living in dormitories, travelers to areas where meningococcal disease is hyperendemic or epidemic, microbiologists working with live N. meningitidis, military recruits, and persons with immunological deficits, such as terminal complement deficiency and functional or anatomic asplenia [82].

The current focus on adolescents is a laudable step toward prevention of meningococcal disease in the United States, although a comprehensive program will require vaccination of infants, the group with the highest risk [84, 85]. Several meningococcal conjugate vaccines that are immunogenic in infants may soon be licensed in the United States; these include a second tetravalent (A/C/Y/W-135) polysaccharide-protein conjugate vaccine that uses CRM197, as the protein carrier [86–88] and a combination Haemophilus influenzae serotype B and serogroup C/Y meningococcal conjugate vaccine with each polysaccharide component conjugated to tetanus toxoid [89]. Outer membrane protein–based vaccines for the prevention of endemic serogroup B disease are also in development for use in the United States and worldwide [90, 91], although these vaccines will probably not be available for several more years. The addition of protection against serogroup B meningococcal disease is crucial because of the importance of disease caused by this serogroup in many countries [1].

UNITED KINGDOM EXPERIENCE WITH SEROGROUP C MENINGOCOCCAL CONJUGATE VACCINES

Because insufficient time has elapsed since the beginning of routine use of MCV4 and because of the low vaccine coverage rates among adolescents, it is not possible to draw conclusions about the eventual impact of routine meningococcal immunization in the United States [83]. However, several recent ex-
Meningococcal disease among unvaccinated persons. The impact, if any, of this vaccine on meningococcal carriage aged 6 months to 5 years [102]. However, no data are available on the impact, if any, of this vaccine on meningococcal carriage among persons who were vaccinated or on the incidence of meningococcal disease among unvaccinated persons.

In summary, the epidemiological profile of meningococcal disease in the United States is highly dynamic and constantly changing. The introduction of MCV4 into the routine immunization schedule for adolescents is a promising first step, but additional work is needed. First, efforts must be made to increase vaccine coverage with MCV4 and with the other vaccines that are now recommended for adolescents. Second, conjugate vaccines for infants, which are likely to be available soon, are required. Finally, broadly protective vaccines that prevent both endemic and epidemic serogroup B disease are needed.

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NEW ZEALAND EXPERIENCE WITH SEROGROUP B VACCINE

In the United States and many other parts of the world, a substantial proportion of meningococcal disease is caused by serogroup B Neisseria meningitidis, which is antigenically highly variable in settings where it is endemic. Unfortunately, no licensed vaccine exists that covers all serogroup B strains. However, epidemics of serogroup B disease are caused by single clones, which has allowed for the development of tailor-made serogroup B vaccines. The incidence of meningococcal disease in New Zealand increased from ~1.6 cases per 100,000 population in 1990 to a peak of 17.4 cases per 100,000 population in 2001. This was the result primarily of the emergence of a sequence type 41/44 clonal complex/lineage 3 serogroup B clone, which accounted for 85% of cases by 2000 [11, 100]. The highest rates of disease occurred among young children, and a disproportionate number of cases occurred in Pacific Islander and Maori children [11].

This epidemic led to the development and introduction of an outer membrane vesicle vaccine against the epidemic strain [101]. The vaccine was initially introduced in mid-2004 in areas of North Island, where the incidence of disease was high, and was further introduced across the country over a period of 2 years. The incidence of meningococcal disease decreased to 2.6 cases per 100,000 population by 2007, and the estimated effectiveness of the vaccine was 80% in fully immunized children aged 6 months to <5 years [102]. However, no data are available on the impact, if any, of this vaccine on meningococcal carriage among persons who were vaccinated or on the incidence of meningococcal disease among unvaccinated persons.


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