Meningococcal Disease and Quadrivalent MenACWY-CRM Vaccine (Menveo®)

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Meningococcal Disease, manifesting as meningitis and septicemia, is a life-threatening bacterial infection that results in significant morbidity and mortality, particularly in childhood. Its epidemic potential and limited opportunities for clinical intervention due to its rapid course present unique public health and clinical challenges. Incidence is highest in infants and young children, with a secondary peak of risk in adolescents. Approximately 10% of cases are fatal and survivors can be left with serious and permanent sequelae including amputations, hearing loss and cognitive impairment. Transmission is only from human-to-human, by infected respiratory tract secretions or saliva and therefore crowding poses a tremendously elevated risk for disease development. Military recruits and university students are at high risk due to the high carriage rate in adolescents, their behavior patterns and close contact. Menveo® (Novartis Vaccines and Diagnostics), a novel quadrivalent meningococcal conjugate vaccine directed against meningococcal serogroups A, C, W-135 and Y, has been shown to be immunogenic and well tolerated in all age groups and was recently licensed for use in Korea. Recent cases and deaths among military recruits drew public attention to their elevated risk and the Korean government has recommended vaccination of all new military recruits. Many Korean students seek to attend school, university, or language institutes in countries where routine meningococcal vaccination is required – clinicians should be aware of such requirements to ensure that students are vaccinated prior to arrival in the destination country. (Korean J Pediatr Infect Dis 2012;19:89-110)

Key Words : Meningococcal disease, Meningococcus, Meningococcal vaccine, Student health

Introduction

Pneumonia, meningitis, septicemia and other potentially life-threatening bacterial infections are leading causes of morbidity and mortality in childhood, particularly in low-resource countries. Historically, the three principal agents of invasive bacterial infection in children have been the polysaccharide encapsulated bacteria: *Haemophilus influenzae* type b (Hib), causing Hib meningitis and pneumonia;

Streptococcus pneumoniae, causing pneumococcal meningitis, pneumonia and other invasive disease (IPD); and *Neisseria meningitidis*, causing meningitis and acute septicemia or meningococcemia[1]. The course of meningococcal disease differs from Hib or pneumococcal disease in important ways that present unique public health and clinical challenges. First is its epidemic potential; although Hib and pneumococcal infections occasionally cluster within groups of people sharing close contact, secondary cases and outbreaks predictably follow index meningococcal cases, especially among household members, but also among attendees of daycares, schools and universities, military recruits, travelers – on shared conveyances or in mass gatherings, such as in the

Hajj pilgrimage, and even among entire communities such as in the 'meningitis belt' of Africa[2]. Contacts of cases in such situations require antibiotic prophylaxis and even single cases can excite public panic while clusters of cases frequently necessitate mass vaccination[3-5]. Secondly, the opportunity for clinical intervention after meningococcal infection is more limited because the disease progresses so quickly, leaving little time between disease onset and diagnosis to life-threatening illness and even death[6]. The incidences of both invasive Hib and pneumococcal disease have fallen dramatically with the introduction of vaccines in the last 30 years, although the story of pneumococcal serotype replacement still is unfolding[7, 8]. These successive public health triumphs rouse great anticipation for the introduction of new meningococcal vaccines to control a perhaps less common but more feared disease.

Meningococcal disease

N. meningitidis is a gram-negative diplococcus with an outer membrane comprising functional proteins and lipo-oligosaccharide (LOS) and, in pathogenic strains, a polysaccharide capsule external to the outer membrane. The polysaccharide capsule is a principal virulence factor and anti-capsular antibodies are bactericidal and protective. Although 13 immunologically distinct capsular serogroups of *N. meningitidis* have been identified, six serogroups (A, B, C, W-135, X and Y) account for most cases of disease[2].

N. meningitidis is transmitted only from human-to-human, by infected respiratory tract secretions or saliva via airborne respiratory droplets or shared fomites, and usually only under conditions of close personal contact. Dry environmental conditions favor the organism's survival and transmission. After exposure, the organism colonizes the nasopharynx, leading to usually brief, self-limited carriage that lasts for weeks but sometimes months[9]. The vast majority of people remain asymptomatic and clear the bacteria, but in certain individuals bacteria penetrate the mucosa and invade the bloodstream where they proliferate and disseminate rapidly in a systemic infection[10]. Alterations of the respiratory mucosa by antecedent viral infection, including influenza, dry air, and cigarette smoking may increase the risk for invasive infection. Illness usually occurs shortly after the organism is acquired, within 1-14 days[2]. The contribution of host genetic background to the risk of developing clinical disease (as well as risk for severe disease) has been shown for complement and properidin deficiencies while genome wide association studies have identified polymorphisms in the *CFH* gene region as contributing to reduced risk[11-15]. Although considerable attention has been focused on polymorphisms in mannose binding lectins as a risk factor, a recent analysis concluded that the association remains unproven[16].

Clinical features

Meningococcal disease is diabolical in that the prodrome is nonspecific with vague symptoms that may mimic those of a common viral infection, misleading the clinician of the much more serious and sometimes catastrophic illness that will follow. Often it is not until the appearance of meningeal signs or a non-blanching petechial rash, the cutaneous hallmark of meningococcemia, that a specific diagnosis

is suspected. The evolution of illness is so fast that a mildly unwell infant or adolescent can return to the clinic seriously ill or moribund, and progress to a critical stage and death in a matter of hours, outpacing host innate and existing adaptive immune responses and sometimes rendering antibiotic therapy and supportive care futile[10, 17]. Approximately one third of meningococcemia cases develop this rapid and relentless course and overall, approximately 10% of cases are fatal, with higher case-fatality rates among adolescents than in infants. Adding to the burden of disease, recovery can be followed by permanent disabling sequelae. In a study of Canadian patients, the mortality rate of serogroup C meningococcal disease was 14% but a similar percentage of cases (15%) had sequelae, including scars following skin necrosis (12%), amputations (5%), hearing loss (2%), and renal failure (1%)[18]. Reductions in verbal and full scale IQ and intellectual function can occur not only in children with meningitis[19] but also in other recovered children who experienced severe illness and extended ICU stays. Developmental delay and difficult social integration, as well as their impact on families, contribute further to the overall impact of the disease.

Interestingly, brief bacteremias can be cleared spontaneously in some individuals whose unsuspected infection was detected by chance in blood cultures while, in others, with so-called "chronic" meningococcemia – which in reality runs a subacute course, the illness can smolder for weeks and months with arthralgias and rash, similar to disseminated gonococcal infection[2, 9, 10].

While meningitis and septicemia are the two major manifestations of invasive meningococcal disease, meningitis alone is the presentation in 60% of cases[2, 10]. Bacterial invasion of the meninges leads to a host inflammatory response with an accumulation of polymorphonuclear and other inflammatory cells and local release of cytokines in response to bacteria and shed lipo-oligosaccharide. The blood brain barrier may be impaired by inflammatory mediators but the infection is relatively compartmentalized, with a lower bacterial and endotoxin burden and inflammatory response in blood than in the cerebrospinal fluid. However, infection and inflammation in that anatomically confined compartment lead to brain edema and elevated intracranial pressure, resulting in headache, nausea, vomiting, neck stiffness, impaired consciousness, photophobia, and seizures, and in small infants bulging fontanelles[6, 10]. The case-fatality rate in meningitis cases is lower than in patients with septicemia, but recovery can be followed by serious and permanent sequelae. For example, neurocognitive testing performed in the context of a recent case-control study in U.K. showed that, on average, children who had survived serogroup B meningococcal disease had significantly lower full scale, verbal and performance IQ, had lower scores on tests measuring memory, planning and organization and were more likely to have psychological disorders than age- and gender-matched controls (Table 1)[19].

Septicemia is the most devastating form of invasive meningococcal infection and occurs in approximately 40% of cases. The rapid proliferation of meningococci in blood results in a high bacterial load and elevated concentrations of endotoxin leading to shock and disseminated intravascular coagulation (DIC)[2, 10]. The initial symptoms include high fever, cold hands and feet, malaise, lethargy, poor feeding, leg pains and abnormal skin color[6]. Within a few

hours of the initial signs, patients develop impaired pulmonary, renal, and adrenal function, septic shock and DIC with thrombotic lesions diffusely − in the skin and limbs (purpura fulminans), kidneys, adrenal glands, choroid plexus, and lungs. Septicemia is associated with a high rate of mortality and, in survivors, sequelae caused by endovascular inflammation and thrombosis: skin necrosis that can necessitate skin grafts; and purpura fulminans necessitating amputation of digits or whole limbs. The most feared outcome is rapid evolution to death due to adrenal necrosis − Waterhouse−Friedrichson syndrome.

Diagnosis and treatment

Although confirmation of a specific microbiological diagnosis is needed to guide both therapy and public health responses, in the context of a high clinical suspicion, empirical penicillin therapy can be life−saving and is recommended in situations of hyper−endemic and epidemic transmission. Gram stains of cerebrospinal fluid (CSF) or petechial lesions can provide an immediate presumptive diagnosis. A specific diagnosis usually is made by recovering the organisms from blood, CSF, or other usually sterile site; however, compared to diagnosis by PCR, bacterial cultures are relatively insensitive, and half to two thirds of cases may be missed. Primers directed against the capsular transport gene usually are used although assays employing primers for the super−oxide dismutase gene can detect additional cases. As more primary diagnostic laboratories turn to PCR for diagnosis, it is important to note that attempts still should be made to isolate and retain the organism so that they can be characterized for scientific and epidemiological purposes.

Because of the rapid evolution of invasive infection, therapy should be instituted based on a clinical diagnosis. When meningococcal C disease was epidemic in the UK, general practitioners were urged to carry penicillin in their bags so they could institute presumptive therapy. Meningococcus remains sensitive to penicillin although sporadic resistant strains have been reported[20]. However, antibiotic resistance has become important in the context of contact chemoprophylaxis; quinolone resistance has become widespread in the U.S. so that it is no longer recommended for chemoprophylaxis and rifampin and ceftriaxone

Table 1. Psychometric Testing in Recovered Cases of Serogroup B Meningococcal Disease

Measures	Case	Control	P−value
Full scale IQ*	99.1	106.6	<0.0001
Verbal IQ*	100.3	107.5	<0.0001
Performance IQ*	97.7	105.2	<0.0001
Working memory[†]	95.8	103.9	<0.0001
Planning and organization[†]	15.8	18.2	0.008
Psychological disorders[†] (N,%)	61, 26%	33, 10%	<0.0001

Note: Data are mean scores, unless otherwise stated. IQ, intelligence quotient.
*Wechsler pre−school and primary scale of intelligence (WPPSI) for participants aged 3−6 years, or the Wechsler abbreviated scale of intelligence (WASI) for those aged 7 years or older.
[†]Children's Memory Scale, for participants aged 5 years or older and Rey Osterreith complex figure test for those aged 6 years or older.
[†]Parental completion of the Strengths and Difficulties questionnaire (all ages).
Source: reference[19].

are used[20]. In Korea and other countries with prevalent *Mycobacterium tuberculosis* infections, fluoroquinolone resistance may be elevated due to the drug's widespread chronic use in tuberculosis treatment and prophylaxis[21].

Epidemiology

Endemic meningococcal infections are cosmopolitan among humans— there is no animal reservoir. Although the WHO has estimated that 500,000 cases occur annually worldwide, there appears to be a secular trend toward declining incidence in developed countries, independent of the introduction of routine vaccination [22]. In the United States, meningococcal disease incidence has reached a historical low, below 0.5/100,000 in the general population; however, age-specific incidence rates in infants remain high, with a secondary peak of risk in adolescents and young adults. Forces behind the secular decline have not been defined, although it has been noted that a reduction in cigarette smoking can be linked ecologically. The quality of meningococcal disease surveillance is inconsistent regionally but, in many countries it is limited by laboratory diagnostic capacity. Epidemiological studies, however, show continued high incidence rates in some regions, especially in Africa, where transmission of group A and more recently, group W-135 and X cases recur in outbreaks, with rates far exceeding the 10/100,000 epidemic threshold. In the context of other infectious disease, its case fatality rate of 10% is high and it is usually higher in developing countries where diagnosis and treatment are more limited[1, 20, 23]. In temperate locations, meningococcal disease exhibits a seasonal pattern of elevated incidence during the winter and spring.

Like many bacterial infections, the highest age-specific risk for meningococcal disease is in young children, especially in infants in the first year of life in whom age-specific incidence rates are ~5-10/100,000 (Fig. 1)[24]. A secondary peak of risk, with incidence rates ~1-3/100,000 is seen in adolescents and young adults (11-24 years-old)[25]. Recent trends suggest that the population of older adults form a third age cohort at elevated risk for meningococcal disease. Disease rates for serogroups B, C and Y vary by age, with serogroup B accounting for most cases in infants, serogroup C affecting adolescents and young adults, and serogroup Y cases tending to occur more frequently in older adults.

The distribution of subgroups causing meningococcal disease varies greatly by country and region and is also subject to relatively rapid change[2, 26, 27]. It is remarkable that despite the adage that infectious diseases know no borders, in the U.S., serogroups B (23%), C (31%) and Y (35%) are similarly distributed, while in Canada, endemic serogroup B cases (43%) have been responsible for most infections, with lower rates for serogroups C (25%) and Y (22%)[27]. Provincial programs of vaccination against group C disease has led to control of that serogroup, leaving serogroup B as the predominant cause of meningococcal disease. Serogroup distribution can be even more geographically delimited as illustrated by the hyperendemic clonal transmission of serogroup B infections that is limited to Oregon among the U.S. States. Similarly, serogroups C and B exhibit sharp differences in incidence among geographical areas within Brazil and serogroups A and B in different states of South Africa[28].

Globally, the highest incidence of meningococcal

disease is seen in the 'meningitis belt' of sub-Saharan Africa, in which recurring outbreaks of serogroup A disease have been associated with attack rates as high as 1000 per 100,000[27]. Disease epidemiology has changed in the region, with evidence of increasing numbers of cases and outbreaks due to serogroups W-135 and X[27]. In European countries, hyperendemic and epidemic transmission of serogroup C disease in the 1990s - especially in the UK, led to introductions of monovalent meningococcal C conjugate vaccines to national vaccination schedules of most countries, leading to the virtual disappearance of cases due to that serogroup[27]. Serogroup B is now responsible for the great majority of all cases, with Y and W-135 contributing a considerably smaller share[29]. A recent trend towards increasing cases of serogroup Y has been observed in several countries, however, including Sweden (51%), Finland (21%), Norway (55%), Switzerland (22%), Italy (11%), Netherlands (17%), Germany (7%), and Denmark (6%)[30]. In Asia the epidemiology of meningococcal disease is not as well described, although outbreaks periodically come to attention e.g. in the Philippines and India in 2005. Disease surveillance in China has been more systematic and has documented the recent emergence of serogroups B and C and diminishing cases due to serogroup A which had been predominant for decades, often occurring in epidemics[31]. Increasing endemic transmission and outbreaks of serogroup C disease in southern China have led to the use of combined serogroup A and C vaccines in EPI programs in some provinces. Serogroup B dominates in Taiwan and Japan[31]. In India, Bangladesh, Mongolia, Pakistan, Nepal and Philippines, surveillance is poor although most reported cases are due to serogroup A[31].

The highly dynamic patterns of serogroup distribution that can undergo shifts over relatively short periods of time is well illustrated by the increase of serogroup Y disease in the U.S. which increased over
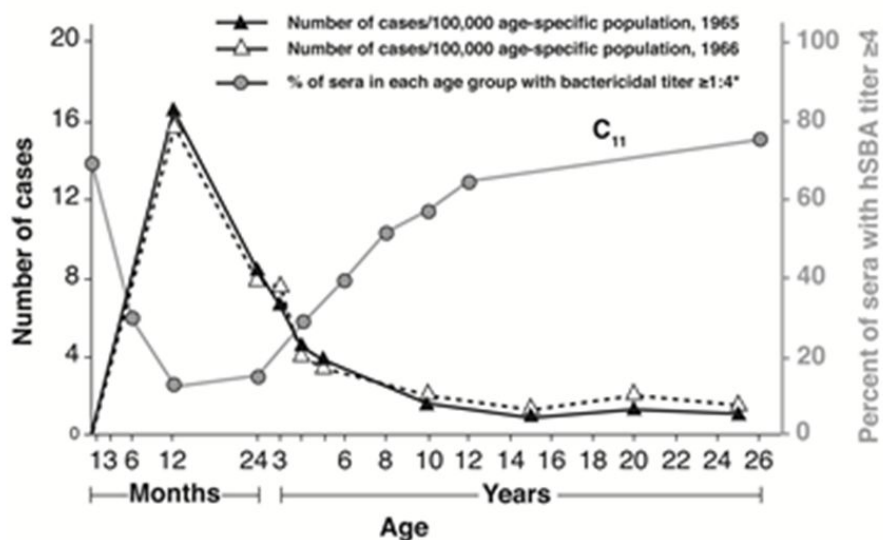

Fig. 1. Age-specific incidence of meningococcal disease vs. serum bactericidal antibody.
Source: adapted from reference[24]. © 1969 Rockefeller University Press. Originally published in Journal of Experimental Medicine. 129:1307-26. doi: 10.1084/jem.129.6.1307.

a period of 20 years, from causing a few percent to about one-third of cases[27]. A similar change in the distribution of serogroup Y occurred in Colombia [27]. Turkey has seen a shift from serogroups A and C to B and W-135[32] while in the Czech Republic, serogroup C is increasing[33]. In Saudi Arabia, serogroup W-135 emerged and surged within two years in a sudden outbreak among Hajj pilgrims who spread the strain globally, including to the UK where local transmission led to community outbreaks for a period of time, and to areas of Africa where the strain became entrenched and continued to spread more broadly in endemic and epidemic forms[26, 27]. The unpredictability of serogroup distribution is a strong argument in support of the use of vaccines with broad serogroup coverage.

In Korea, a study of bacterial meningitis occurring between 1996 and 2005, described 401 cases of which *N. meningitidis* was the third most common cause, following *S. pneumoniae* and Hib. *N. meningitidis* was responsible for 4.5% of cases with a case-fatality rate of 16.7%[34]. A 2 year International Vaccine Institute study of the causes of bacterial meningitis in children <5 years old in China, Vietnam

and Korea showed that meningococcus caused approximately 2.6% of cases in Korea, a proportion similar to that found in China and Vietnam. The serogroup distribution of cases in Korea was limited to C, X, and Y (Table 2)[35]. Other reports suggest a more diverse circulation of meningococcal serogroups in Korea, including W-135 and B[31, 36]. Early carriage studies in army recruits indicated that serogroup W-135 predominated and a recent death and outbreak were attributed to W-135[37]. The circulation of diverse meningococcal serogroups underscores the need for broad vaccine coverage in Korea.

High-risk populations

Although most cases of meningococcal disease occur in healthy persons without previously identified risk factors, certain biological attributes and behaviors are associated with increased risk for acquiring the disease. Infants under 6 months of age are at high risk because of increased susceptibility associated with a still developing immune system. They may be passively protected in some circumstances by maternal antibodies but protection is not uniform, as

Table 2. Serogroup Distributions of *N. Meningitidis* in Cerebrospinal Fluid (CSF) Specimens in Children Aged <5 Years old in China, South Korea, and Vietnam

	China	Korea	Vietnam	Total
Confirmed by PCR (N)	67	92	125	284
Sequenced to confirm serogroup (N)	6	16	22*	44
A (N, %)	0	0	0	0
B (N, %)	0	0	2 (9.1)	2 (5.0)
C (N, %)	0	1 (6.3)	20 (90.9)	21 (48.0)
W-135 (N, %)	1 (16.7)	0	0	0
X (N, %)	3 (50.0)	9 (56.3)	0	12 (27.0)
Y (N, %)	2 (33.3)	6 (37.5)	0	9 (20.0)

Surveillance periods: China, January 1, 2000-December 31, 2002; South Korea, September 1, 1999-December 31, 2001; Vietnam, March 4, 2000-March 3, 2002. Of 2032 CSF specimens tested, 284 were confirmed by PCR and 44 specimens underwent sequencing to confirm serogroup.
*One specimen could not be linked with the clinical database.
Source: adapted from reference[35].

illustrated by the high rate of serogroup B disease in infants under 6 months of age. Less attention has been directed at the increased age-specific risk of meningococcal disease in older adults, presumably associated with immunosenescence, which is in a similar range as the age-specific risk in adolescents. Inherited complement deficiencies lead to a high risk for repeated infection. While generally rare, in some populations (e.g. South Africa), the population prevalence of such disorders can be considerable, to the extent that population wide screening has been proposed[12]. Physiologic complement deficiency also can be acquired, most notably, resulting from treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome and other alternative complement pathway-associated disorders with eculizumab, which renders these individuals functionally complement deficient and places them at elevated risk for meningococcal infection[38, 39]. The product's package insert therefore requires treated individuals to be vaccinated with meningococcal vaccine. Although the cumulative number of such patients is so far small, indications for the antibody are broadening and clinicians should be mindful of the risk. Functional and anatomic asplenia and implanted cochlear implants are other recognized conditions that increase risk for acquiring infections from encapsulated bacteria, including meningococcal disease. Among other immunodeficiencies, HIV/AIDS is associated with increased risk of acquiring infection and even repeated infection and outbreaks among groups of HIV-infected individuals have been reported[40].

Numerous behavioral factors are associated with risk of acquiring the disease. These include acquired host factors that compromise the respiratory mucosal barrier and behavioral factors that increase risk for exposure to the organism. Among the former, smoking and antecedent respiratory tract infection — including influenza, have been well documented to increase the risk for acquiring and developing meningococcal infection, and dry air in the wintertime and during the dry season in locations such as the African meningitis belt, have been speculated to compromise local mucosal barriers, facilitating bacterial invasion[27].

Close contact, especially as a household member of a case or in dormitory settings, poses a well-documented and tremendously elevated risk for developing the disease. For household contacts, the relative risk for developing a secondary case is 500-1,000 fold higher than the incidence in the general population. The increased risk is due to a combination of close direct contact resulting in exposure to infected respiratory secretions and shared fomites, thus household contacts are always recommended to be given chemoprophylaxis to eliminate or prevent carriage. Similarly, university students and military recruits are also at high risk, devolving from the high carriage rate that is seen in adolescents — up to 25%, and their patterns of behavior and close contact[2, 27, 41, 42]. The speed at which university students are exposed to and acquire meningococcus is remarkable. A study from Nottingham University showed that within 3 days of the start of the school term, the carriage rate of incoming first term students rose from 6.8 to 11.2% in one day, to 19% in the next day and to 23% one day later, more than 3 fold from 6.8 per cent to 23% in the first three days of the university term[43]. Carriage rates rose as high as 30% to even 70% later in the term.

The factors that account for this rapid acquisition of carriage include male gender, smoking, visiting

bars frequently, living in a mixed sex residence hall, visiting night clubs, and kissing. In a multivariate analysis, students who smoked and also kissed had the highest carriage rates — one third of these students became carriers; those who either smoked only or kissed followed, and those who neither smoked nor kissed had the lowest risk. However, in all groups — including the nonsmokers who did not kiss, carriage was independently associated with increased pub visitation. This indicates that the social mixing in pubs alone was sufficient to increase carriage, independent of the other factors and underscores the importance of close social interactions, in which nearly all students engage, toward the risk for acquiring meningococcal carriage.

The risk among military recruits who live in barracks and train together in close quarters is similar: in the U.S. army between 1964 and 1970 when no meningococcal vaccines were routinely used, outbreaks among recruits led to rates of meningococcal disease hospitalization of 23.6 cases per 100,000 person-years (Fig. 2)[42]. Vaccination campaigns were started in 1972, initially with a monovalent C polysaccharide vaccine, then with bivalent AC polysaccharide vaccine, and finally with polysaccharide followed by conjugate quadrivalent vaccine (containing polysaccharides of serogroups A, C, Y, and W-135), leading to a reduction of hospitalization rates to 1.4 cases per 100,000 person-years between 1983-1998[42].

In Korea, where military service is compulsory for men, a total of 12 cases of meningococcal disease were reported between August 2000 and July 2001, for an annual incidence of 2.2 per 100,000, a rate that is similar to the risk for U.S. college students which ranges from 2.3 to as high as 5.1 per 100,000 for those freshman living in dormitories[36, 41]. Recent cases and deaths in recruits have drawn public attention to the elevated risk for disease and outbreaks among draftees. Accordingly, the Korean government has recently recommended vaccination of all new military recruits.
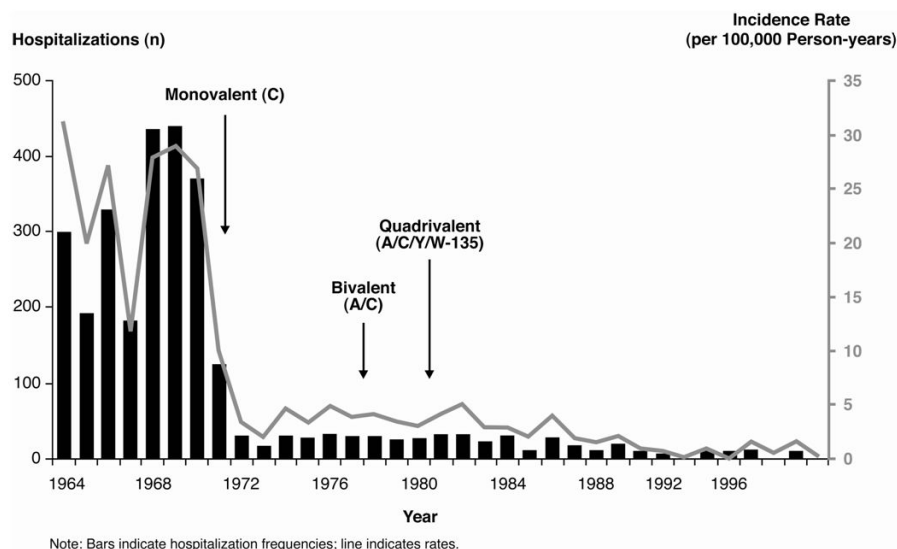

Fig. 2. Meningococcal disease in U.S. military, 1964-1998, and impact of vaccine introductions.
Source: adapted from reference[42], by permission of Oxford University Press.

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Meningococcal vaccines

The principal protective antigen of meningococcus – like other encapsulated bacteria such as Hib and pneumococcus – is the polysaccharide capsule. Chemical structural and hence antigenic differences of respective capsules define their serogroup[1, 2]. However, other surface expressed proteins also can play a role in protection and are being exploited in candidate vaccines against group B meningococcus. Although serogroup B accounts for a major proportion of cases in many countries, the development of a vaccine containing this serogroup has proved challenging. The B capsular polysaccharide is cross-reactive with human neural antigens and is therefore poorly immunogenic; moreover, the cross reactivity leads to a risk of molecular mimicry that could cause autoimmune damage. Therefore, an anti-capsular vaccine is not a viable approach and protein based vaccines are under development[44].

Although vaccines can be made from bacterial polysaccharides alone, their conjugation to a carrier protein results in much better and more useful immunogens. Glycoconjugate vaccines, in contrast to plain polysaccharide vaccines provide higher levels of antibodies that also are more persistent. Importantly, conjugate vaccines are immunogenic in infants under two years of age while plain polysaccharide vaccines, in general, are not. Glycoconjugate vaccines have the important property of reducing carriage and the responses are boostable. Like some Hib and pneumococcal conjugate vaccines, the ACWY vaccine that has recently been licensed in Korea (Menveo®) employs CRM197, a nontoxic mutant form of diphtheria toxin, as the carrier protein that is chemically linked to the respective purified polysaccharides[44].

The low incidence of meningococcal disease makes it impractical to conduct prospective clinical trials to evaluate vaccine efficacy[22]. However, a serological correlate of protection based on the presence of serum bactericidal antibodies (SBA) in vaccinees has been accepted by regulators. Thus licensure is based on demonstrating that SBA titers at protective levels are achieved in a sufficient proportion of vaccinated subjects[22]. The rationale for accepting a serological correlate of protection comes in part from the observation that the age-specific risk of meningococcal disease in infants varies inversely with their level of bactericidal antibodies[24]. Bactericidal antibodies with SBA titer ≥ 4 are high at birth due to maternally derived antibodies; the levels decline as passively derived maternal antibodies turn over, and rise again, as the infant develops his/her own antibodies (Fig. 1)[24]. Thus, the risk of disease is a mirror image of the decline and rise of protective antibodies, indicating that SBA titer ≥ 4 are protective. More precisely, in studies among military recruits, individuals who had pre-existing SBA titers of ≥ 4 exhibited a significantly lower risk for developing disease in subsequent outbreaks than those with a lower titer[24].

In the SBA assay, fresh complement is added to facilitate killing of the bacteria by antibody in the test serum sample. The assay is performed by adding bacteria to serum dilutions with fresh complement; the mixtures are incubated and then plated onto agar plates where bacteria that are not killed form colonies. These are counted to arrive at the serum dilution endpoint titer. Both human and rabbit complement have been used in the SBA assay to demonstrate immunogenicity for the licensure of me-

ningococcal vaccines in the U.S. and EU. SBA titers measured with human and rabbit complement are not directly comparable but complement-dependent bactericidal activity can be reliably measured regardless of the complement source[46].

Plain polysaccharide meningococcal monovalent A and subsequently bivalent AC vaccines were developed and deployed initially in military populations, and have been used in specific circumstances to control hyperendemic disease in civilian populations e.g., group A outbreaks in Africa and China, and group C disease in Canada. When group C meningococcal disease became hyperendemic in the U.K. and elsewhere in Europe in the 1990s, and recognizing the limitations of plain polysaccharide vaccines, monovalent group C conjugate vaccines were developed, approved and deployed in national programs with great urgency, leading to what can be regarded as a public health triumph in disease control. The speed with which the outbreak was halted in the U.K. was shown to be due, in part, to reduced carriage of the organism through mass catch-up vaccination that included adolescents and young adults. Thus, the overall reduction in disease incidence resulted from both direct protection of the vaccinated infants and children but also reduced transmission of the organism due to its elimination from carriage, with an overall vaccine effectiveness of ~97%[47].

This combined impact underscored the benefit of herd protection among other advantages of conjugate over plain polysaccharide vaccines. Similar success was seen in other countries with hyperendemic group C disease that deployed the conjugate vaccine, including Canada and Australia with an overall effectiveness (that included both direct and indirect effects) of ~87%[48].

Importantly, in contrast to the experience of serotype replacement of pneumococcal serotypes not included in the seven valent pneumococcal conjugate vaccine, no widespread serogroup replacement has been seen in the wake of mass meningococcal group C vaccination campaigns, although individual examples of capsular switching have been noted.

In the U.S., where serogroup C organisms caused a smaller proportion of cases and that had a much lower rate of meningococcal disease overall compared to Europe, plain ACWY polysaccharide vaccine (MPSV4, Menomune®, Sanofi Pasteur) was licensed for use principally in high risk individuals, travelers, and adolescents - particularly those entering colleges and universities where sporadic cases occurred at a relatively higher incidence than in the general population. Many universities and individual State laws mandated vaccination prior to enrollment. A quadrivalent conjugate vaccine (MenACWY-D [Menactra®, Sanofi Pasteur], in which the polysaccharides were conjugated to denatured diphtheria toxoid carrier protein) soon followed and, in order to reduce the adolescent cases that formed a secondary peak of meningococcal disease incidence, a routine recommendation for vaccination of all children at 11 years of age was adopted. As described above, the vaccine was licensed on the basis of a serological correlate of protection; however, subsequent post-licensure studies have reported a field effectiveness of 80-85%[51].

Early effectiveness results (>99%) of a newly launched CRM conjugate serogroup A vaccine developed for use in Africa further underscores the rapid direct and indirect impact provided by glycoconjugate meningococcal vaccines[50]. Although the highest age-specific rate of meningococcal disease

occurs in infants, no vaccine currently is licensed for that age group, although conjugate serogroup ACWY vaccine and protein-based group B vaccines are close to licensure in some countries; meanwhile, where population-wide vaccination has been deployed, herd effects have provided indirect protection of that age group against strains contained in the vaccine.

Novartis' meningococcal vaccine

MenACWY-CRM (Menveo®; Novartis Vaccines and Diagnostics) is a novel quadrivalent meningococcal conjugate vaccine directed against serogroups A, C, W-135 and Y in which the purified polysaccharides are chemically conjugated to the carrier protein CRM197. MenACWY-CRM is an adjuvant- and preservative-free formulation in which the lyophilized serogroup A portion (which is inherently unstable and undergoes hydrolysis) is reconstituted with the liquid portion containing the conjugates of the CWY polysaccharides, mixed and then administered intramuscularly[51]. MenACWY-CRM has been registered in over 50 countries and more than 5 million doses have been distributed. The vaccine is indicated for 2-55 year olds in the U.S.[51], and Canada, and for adults and children from 2 years of age (with no upper age limit) in Europe, and an increasing number of countries in Asia and South America. In Korea, the vaccine is indicated for persons 11-55 years of age.

More than 26,000 subjects have received MenACWY-CRM in the context of clinical trials performed in all age groups, including infants from 2 months of age. MenACWY-CRM has been shown to be highly immunogenic and well tolerated in infants

[52], toddlers[53], children[54, 55], adolescents[56, 57] and adults[58]. For example, a phase 3 multicenter study conducted in 2180 adolescents (11-18 year olds) in the U.S. compared the immunogenicity and safety of a single dose of MenACWY-CRM with a single dose of MenACWY-D[56]. In comparison to subjects who received MenACWY-D, a significantly higher percentage of MenACWY-CRM recipients achieved hSBA titers ≥8 against serogroups A (67% vs. 75%), W-135 (88% vs. 96%) and Y (69% vs. 88%) and MenACWY-CRM was non-inferior to MenACWY-D with respect to serogroup C (84% each) (Fig. 3)[56]. The hSBA geometric mean titers (GMTs) in response to MenACWY-CRM were significantly higher compared with MenACWY-D, and criteria for superiority were met for all 4 serogroups. Recipients of both vaccines reported similar rates of mild to moderate solicited reactions (64% MenACWY-CRM vs. 70% MenACWY-D). A phase 2 study conducted in 524 U.S. adolescents aged 11-17 years compared the immunogenicity and safety of a single dose of MenACWY-CRM with a single dose of MPSV4. In comparison to MPSV4 recipients, significantly higher percentages of MenACWY-CRM recipients achieved hSBA titers ≥8 against serogroups A (41% vs. 81%), C (61% vs. 84%), and Y (82% vs. 95%) at one month post-vaccination and percentages in the MPSV4 while MenACWY-CRM groups were similar against serogroup W-135 (84% vs. 91%)[57].

Follow-up studies have been conducted to evaluate the persistence of bactericidal antibodies and response to a booster dose of MenACWY-CRM administered in late adolescence. For example, in a 22 month follow-up of the phase 3 study in which adolescents were initially vaccinated with either

MenACWY−CRM or MenACWY−D, a significantly higher percentage of MenACWY−CRM recipients had hSBA titers ≥8 against serogroups A, W−135 and Y[59]. In a further follow−up conducted at 3 years after primary vaccination with MenACWY−CRM or MenACWY−D, a significantly higher percentage of MenACWY−CRM recipients had hSBA titers ≥8 against serogroups W−135 and Y[60]. Response to a booster dose of MenACWY−CRM administered 3 years after primary vaccination with MenACWY−CRM or MenACWY−D elicited a robust immune response against all serogroups and was well tolerated in both vaccine groups: at one month after the MenACWY−CRM booster dose that was administered 3 years after primary vaccination, 100% of subjects initially vaccinated with MenACWY−CRM and 99−100% of those initially vaccinated with MenACWY−D demonstrated hSBA titers ≥8 against all serogroups[60].

One year after adolescents were vaccinated with MenACWY−CRM or the plain polysaccharide vaccine MPSV4, the percentages of subjects with hSBA titers ≥8 against serogroups C, W−135 and Y were significantly higher in subjects who received MenACWY−CRM (77% vs. 61%; 93% vs. 61%; 82% vs. 55%, respectively)[57]. In a further follow−up conducted 5 years after primary vaccination, a significantly higher percentage of subjects initially vaccinated with MenACWY−CRM had hSBA titers ≥8 against serogroups C and Y than in those initially vaccinated with MPSV4[61]. A booster dose of MenACWY−CRM was administered in these subjects 5 years after primary vaccination. In subjects initially vaccinated with MenACWY−CRM, hSBA GMTs were above 1000 against all four serogroups within one week post−booster[61]. Although the anamnestic responses are considered to have a limited role in protecting against illness, the high GMTs achieved with the booster are expected to provide circulating antibodies at protective levels for a long duration. At one month after the MenACWY−CRM booster, 98−100% of subjects initially vaccinated with Men
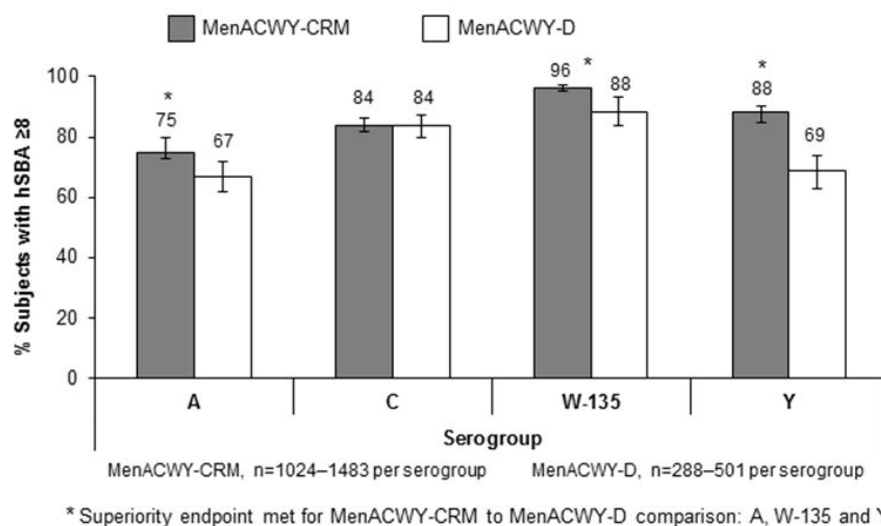

Fig. 3. Comparison of immunogenicity of MenACWY-CRM with that of MenACWY-D per serogroup, one month post-vaccination.
Source: adapted from reference[56].

ACWY-CRM and 84-96% of subjects initially vaccinated with MPSV4 showed with hSBA titers ≥8 across serogroups[61].

In the U.S. and in European countries, tetanus, reduced-dose diphtheria and reduced-dose acellular pertussis (Tdap) and human papilloma virus (HPV) vaccines are recommended for routine use in adolescents. Two differently designed phase 3 randomized controlled trials have evaluated the immune response of MenACWY-CRM when given concomitantly with Tdap in 1072 subjects 11-25 year of age[62] or when given concomitantly or sequentially with Tdap and HPV in 1620 adolescent 11 to 18 year olds[63]. In both the studies, the proportions of participants achieving protective titers (hSBA ≥8) against all four serogroups were non-inferior regardless of the concomitant and sequential administration. Immune responses to Tdap and HPV antigens were also comparable when these vaccines were given alone or concomitantly with MenACWY-CRM. All three vaccines were well tolerated; concomitant or sequential administration did not increase reactogenicity.

Although immunogenicity and safety studies of MenACWY-CRM have been performed in infants and toddlers, the vaccine is not yet licensed in this age group, although approval is being sought. A large pivotal phase 3 open-label study was conducted in infants from 2 months of age in the U.S., Colombia and Argentina. In the U.S. arm of the study, 2-month-old infants were randomized 2:1 to receive four doses of MenACWY-CRM co-administered with routine vaccines (DTaP-HBV-IPV, Hib-TT, PCV7, rotavirus and MMRV) at 2, 4, 6, and 12 months of age or to receive routine vaccines alone[52]. The percentage of infants achieving hSBA titers ≥8 after 3 infant doses ranged from 67% (serogroup A) to 96-97% (other three serogroups). Antibody levels declined 6 months later when the infants were 12 months old, but with the 4th (toddler) dose, 94 to 100% of the infants achieved hSBA titers ≥8[52]. These results demonstrate the robust response to MenACWY-CRM in this vulnerable age group and underscore the importance of a dose in the second year of life. Reactogenicity profiles were similar whether MenACWY-CRM was administered alone or with routine infant/toddler vaccines, demonstrating that MenACWY-CRM can be co-administered with routine infant/toddler vaccines without substantial concern for clinically relevant immunological interference.

Recently, MenACWY-D was licensed in the U.S. for use in infants from 9 months of age. In a study in which infants received 2 doses of MenACWY-D at 9 and 12 months of age, 86-100% of subjects achieved hSBA titers ≥8 against serogroups A, C, W-135 and Y[64]. MenACWY-CRM has been investigated in a similar schedule in U.S. infants from 7-9 months of age and demonstrated similar results[53]. Subjects received 2 doses of MenACWY-CRM at 7-9 months and 12 months and were randomized to receive MenACWY-CRM with or without MMRV or MMRV alone at 12 months. After the 2-doses MenACWY-CRM series, 88 to 100% of the toddlers achieved hSBA titers ≥8[53]. Reactogenicity profiles were similar whether MenACWY-CRM was administered alone or with routine infant/toddler vaccines.

MenACWY-CRM was licensed in Korea following a trial in Korean adolescents and adults. In this multicenter, phase 3, placebo-controlled trial, 450 healthy Korean adolescents and adults aged 11-55 years were randomized to receive one dose of either MenACWY-CRM (N=297) or saline placebo (N=

153)[65]. One month post-vaccination, the percentage of subjects with hSBA titers ≥8 against all four serogroups ranged from 79% (serogroup A) to 94-99% (other three serogroups) (Fig. 4)[65]. A conditional definition of seroresponse was used based on the level of pre-vaccination titers: for subjects who were seropositive (pre-vaccination titers ≥4) at baseline, seroresponse was defined as a ≥4-fold increase over pre-vaccination titers whereas for subjects who were seronegative (pre-vaccination titers <4) at baseline, seroresponse was defined as post-vaccination titers ≥8. Overall seroresponse rates were 76%, 86%, 28% and 69% against serogroups A, C, W-135 and Y[65]. A post-hoc analysis carried out in subjects who were seronegative at baseline showed seroresponse rates of 76%, 96%, 84% and 89% against serogroups A, C, W-135 and Y, respectively[65]. This sub-analysis was highly relevant in the clinical context by showing that seronegative subjects — who are the most important to protect since their pre-vaccination hSBA titers were below putative protective levels — responded

adequately to the vaccine.

Meningococcal vaccine recommendations

In most European countries, Canada, Australia, New Zealand, China and many countries in Latin America, rates of pediatric or adolescent meningococcal disease have been sufficiently high that public health programs of routine childhood and/or adolescent vaccination have been established, principally with monovalent meningococcal C conjugate vaccine or quadrivalent ACWY conjugate vaccines. Programs in Europe, Canada, and Australia were highly successful in controlling hypendemic group C disease to the point of near elimination, while the implementation of customized outer membrane vesicle vaccines led to reduction of clonal outbreaks of group B meningococcal disease in Cuba, Norway, Brazil and New Zealand. Current meningococcal vaccine recommendations in selected countries are shown in Table 3. The variability in age groups and valencies of recommended vaccines reflect the epide-
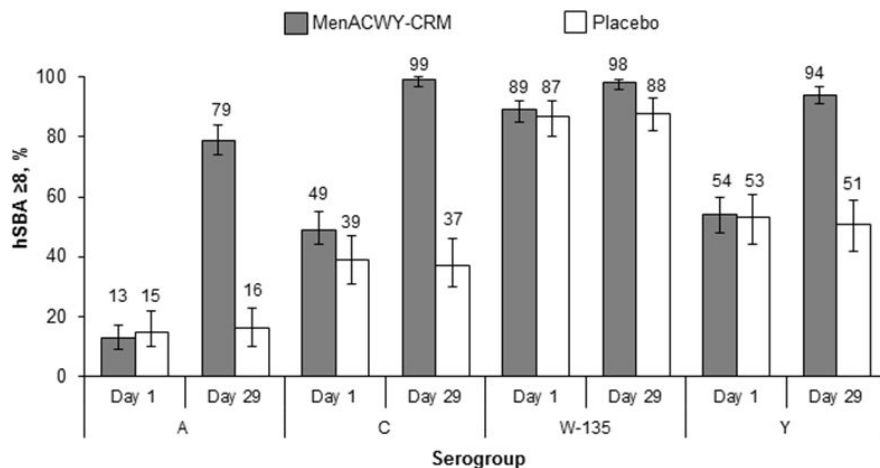

Fig. 4. Immunogenicity of MenACWY-CRM compared with placebo in Korean adolescents and adults, by serogroup, one month post-vaccination. Source: adapted from reference[65].

miological patterns of age-specific risk and serogroup distributions in the respective countries. In the U.S. for example, routine vaccination with a quadrivalent meningococcal conjugate vaccine is recommended for children aged 11-12 years of age with a booster dose at 16-18 years of age, reflecting the increased risk of serogroup C and, to a lesser extent, Y disease in adolescents and especially among freshman university students. In contrast to the pattern of group C disease among children in Europe, Canada and Australia, rates of group C disease in U.S. infants and toddlers are considerably

lower, and routine vaccination for that age group is recommended only for those with risk factors.

Because of the recognized risk of outbreaks in incoming soldiers, mentioned previously, routine vaccination of military recruits also is recommended by Defense Ministries in a number of countries (Table 4), including all tier one NATO countries[66]. Finally, vaccination is recommended in many countries for travelers entering areas with epidemic or hyperendemic transmission (e.g. the meningitis belt of Africa). Quadrivalent vaccine is specifically required (as opposed to recommended) in the unique

Table 3. Meningococcal Vaccination Schedules in Various Countries

Country	Vaccine	Schedule
United Kingdom	MenC conjugate	3, 4, 12 months (combined with Hib at 12 months)
United States	MenACWY conjugate	11-15 years with a booster at 16-18 years
		(2-10 years, 18-55 years if high risk)
Canada*	MenC conjugate	2, 4, 6, 12 months
	MenACWY conjugate	(2-55 years, if high risk)
Australia	MenC conjugate	12 months
China	MenA polysaccharide	2 doses between 6 and 18 months
	MenAC polysaccharide	Booster at 3 and 6 years

*Varies by province.

Table 4. Meningococcal Vaccination Recommendations of Selected NATO Militaries

Country	Military Size	Yearly Recruits	Meningococcal Vaccine Recommendation
United States	1,400,000	250,000	ACWY – Military Recruits, Alert Forces, High-riskdeployments
Turkey	610,000	122,000	A/C – Basic Immunization
France	294,000	58,000	A/C – Basic Immunization
Italy	251,000	50,200	A, C, W-135 – Basic Immunization
Germany	221,000	44,200	A/C – Alert Forces & deployment/travel to risk area
Poland	217,000	43,400	ACWY/NATO
United Kingdom	212,000	42,400	A, C – Deployment/travel to risk area
Spain	166,000	33,000	A, C – Deployment/travel to risk area
Canada	59,000	11,800	A, C, Y, W-135 – Basic Immunizations
Czech Republic	58,000	11,600	A/C– Alert Forces, Basic Immunization
Portugal	45,000	9,000	A,C,Y,W-135 – Deployment/travel to risk area
Belgium	39,000	7,800	A/C – Deployment/travel to risk area
Norway	27,000	5,400	A,C – Deployment/travel to risk area
Denmark	22,000	4,400	A/C – Deployment/travel to risk area

Source: adapted from reference[66].

situation of travel to attend the Hajj[67]. Because of the history of meningococcal A and W−135 outbreaks among Hajj pilgrims, the Kingdom of Saudi Arabia requires proof of vaccination for all pilgrims on entry. Despite concern that other mass gatherings such as the World Cup and Olympic Games might pose a risk for meningococcal disease among attendees, outbreaks have not been reported.

In Korea, a quadrivalent ACWY conjugate vaccine is now licensed for use in adolescents and adults from 11 years of age. Recommendations for the vaccine's use have not yet been promulgated except for routine vaccination of military recruits. However, as many Korean students seek to attend primary or secondary school, university, or language institutes in countries with routine meningococcal vaccine requirements, clinicians, especially pediatricians, should be aware of such requirements to ensure that the students are vaccinated prior to arrival in the destination country.

A survey by the Korean Educational Development Institute (KEDI) showed that, in 2011, almost 300,000 Korean students traveled abroad to study, including universities, graduate school or for language courses (Fig. 5)[68]. The main destination countries included the U.S., England, Australia, Canada, New Zealand and China. In addition, some 30,000 younger children were sent abroad to study in primary and secondary schools.

The KEDI also found that the number of these elementary, middle and high school students is increasing, by 67% in the last year compared to the previous year. The destination country distribution is important because most of them have recommendations to routinely vaccinate children with meningococcal vaccine, either during infancy or as adolescents. Men C vaccine is recommended on the national schedules of England and Wales, Canada, and Australia and also most European countries. New Zealand previously recommended and only recently
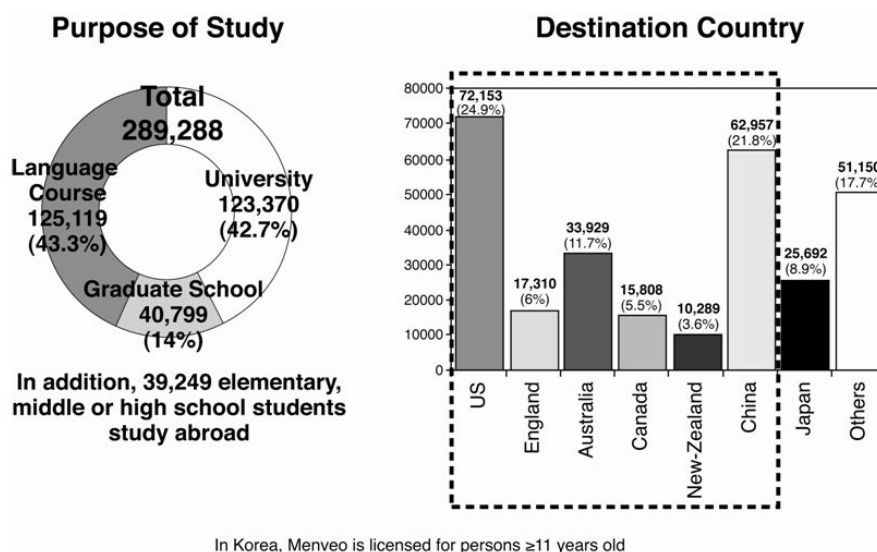

Fig. 5. Korean Educational Development Institute survey of Korean students traveling internationally for courses of study, by purpose of study and destination country, 2011.
Source: adapted from reference[68].

discontinued routine immunization with a custom MenB vaccine. China recommends infant MenAC vaccine on its EPI schedule while the U.S. and Canada recommend ACWY vaccine for adolescents. The U.K. is also moving toward an adolescent men C booster.

Finally, in the U.S., independent of public health recommendations, most universities and many state laws require proof of meningococcal vaccination before students can register for classes, or a waiver letter, indicating that vaccination has been discussed and declined. Nineteen U.S. states also require proof of immunization prior to middle school and high school entry (Fig. 6)[69].

The implication of these recommendations and requirements is that Korean children and adolescents enrolling as students in one of these countries may be denied school entry without proof of vaccination.

To prevent difficulties with local regulations that can change with new legislation, students should be vaccinated prior to departure and should be given evidence of vaccination to present to school officials. From a clinical perspective, unless vaccinated, the visiting student will be unprotected against a risk of meningococcal disease that is considered high enough that classmates surrounding him or her will have been vaccinated with a meningococcal vaccine, either with Men C or ACWY or both. Because the serogroup distribution of disease in these countries varies, vaccination with the licensed quadrivalent vaccine is prudent. Although nearly 2 million students study at home in Korean universities, with more than 300,000 living in dormitories, there currently is no recommendation to vaccinate them upon school entry (Table 5)[70].
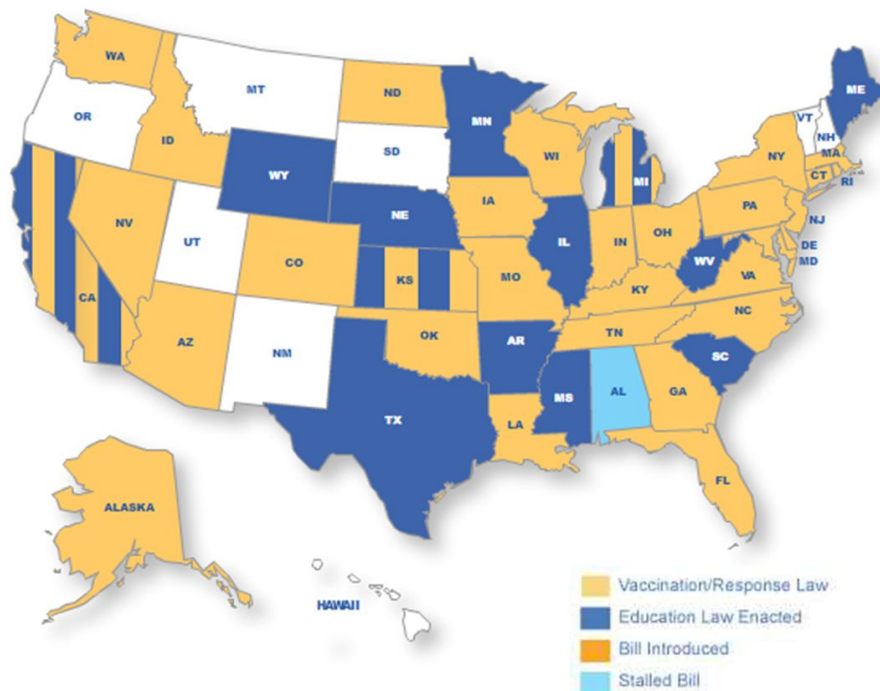

Fig. 6. State laws pertaining to meningococcal vaccination of students, United States.
Source: reference[69].

Table 5. Korean University Enrollment by Region and Dormitory Residence Status

Region	Dormitory residents	Total students	Proportion in dormitories
Seoul	48,164	438,423	11%
Busan/Ulsan/Gyoungnam	47,590	311,222	15%
Daegu/Gyoungbuk	55,677	254,137	22%
Incheon/Gyounggi	46,915	303,951	15%
Gwangju/Jeonnam/Jeonbuk	50,301	248,840	20%
Daejeon/Chungnam/Chungbuk	86,156	382,667	23%
Jeju	2,998	19,627	15%
Total	337,801	1,957,867	17%

Source: adapted from reference[70].

Conclusions

Invasive meningococcal disease caused by *N. meningitidis* is a public health concern in many countries globally, including in the Republic of Korea. Worldwide, an estimated 500,000 cases are diagnosed each year, 50,000 of which are fatal, and others surviving with serious neurological and disabling sequelae[26]. Due to the rapid progression of the disease, which can result in shock and even death within hours, arriving at a correct diagnosis in time to render effective therapy is a clinical challenge. Vaccination can prevent the disease and has been shown to be highly effective in military recruits and in national public health programs.

Because the meningococcal serogroups causing disease vary in time and place and can shift unexpectedly, a quadrivalent ACWY meningococcal conjugate vaccine providing broad coverage is generally preferable to monovalent and bivalent formulations. The MenACWY−CRM vaccine license in Korea, has been shown to be highly immunogenic in all age groups from infants to older adults, providing persistent immunity for ~5 year, and is well tolerated. It has been shown to be compatible with routinely administered childhood and adolescent vaccines. Because meningococcal vaccine is required or recommended for school or university entry in many countries, Koreans enrolling as students in those countries should be vaccinated prior to departure. Vaccination of other persons with high risk medical conditions such as complement deficiency, asplenia and recipients of eculizumab, or who are at high risk for infection, such as military recruits and residents of university dormitories can help prevent these individuals from the devastating impact of invasive meningococcal disease.

Acknowledgements

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