Travelers’ Protection Against Meningococcal Disease: A New Vaccine Option

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Compared with other infections, such as yellow fever or malaria, awareness of the potential for travelers to contract meningococcal disease is low. Global disease incidence rates, however, may be as high as 1,000/100,000 population in the “meningitis belt” of sub-Saharan Africa and are generally between 100 and 800/100,000 population during epidemics in Africa.1,2 In the United States, the annual incidence is 0.5 to 1.1/100,000 or about 1,400 to 2,800 cases annually.3

Although the highest disease incidence is in infants, in many regions and countries, a second peak occurs in the 14- to 25-year-old demographic. Surveillance data from 1999 to 2008 estimated the highest rates of meningococcal disease incidence in the United States were in children aged 4 years and younger (∼2/100,000 population) and adolescents aged 15 to 19 years (∼1/100,000 population).4

In addition to consideration of the disease incidence, it is also important to consider the impact of meningococcal disease on the patient. Onset of meningococcal disease is often sudden and the rate of progression is unpredictable. Initial symptoms are nonspecific and can resemble those of other common and/or benign diseases.5 Therefore, it may be difficult to identify and treat the disease quickly. Invasive disease may develop 1 to 14 days after acquisition of meningococci.6 Despite the availability of appropriate treatment and intensive care, up to 10% to 14% of persons in the United States and 5% to 10% of persons worldwide who contract meningococcal disease die, with a rate of ∼40% among patients with meningococcal sepsis.5,7 Additionally, 11% to 19% of persons who survive meningococcal disease can suffer from permanent disabilities, including brain damage, hearing loss, limb loss, or learning disabilities.5,7 The rapid progression and devastating consequences of disease make prevention through vaccination the best option for controlling meningococcal disease in the community.

For travelers, the risk of contracting invasive meningococcal disease depends on their destination, duration of travel, and behavior while at their destination. For example, Hajj pilgrims (for whom vaccination is required),8 travelers spending extended stays in areas where disease is epidemic or hyperendemic, and those having a high degree of interaction with local communities at risk are all at increased risk for contracting meningococcal disease.9 Guidance on vaccinating travelers against meningococcal disease is provided by national health authorities as well as the World Health Organization (WHO) and, in recent years, has been updated to reflect the development of multivalent meningococcal conjugate vaccines. For example, the Canadian Committee to Advise on Tropical Medicine and Travel (CATMAT) and the UK Joint Committee on Vaccination and Immunization have recently updated guidance on the rationale and recommendations for travelers. A detailed discussion of meningococcal disease vaccination travel requirements and recommendations is presented in the article by R. Steffen in this supplement.

The incidence and distribution of the *Neisseria meningitidis* bacteria serogroups that cause the majority of invasive meningococcal disease—A, B, C, W-135, and Y—vary widely from region to region and country to country and change over time.6,10 The change in distribution of disease-causing *N meningitidis* serogroups, even over relatively short periods of time, is quite unpredictable. In Europe, serogroups B and C cause the majority of disease; in Africa, serogroup A is predominant, along with C and W-135; and, in recent years, a growing proportion of meningococcal disease in the United States is attributable to serogroup Y.1,6,11

A meningococcal vaccine that provides broad protection against multiple serogroups is required to ensure the highest level of protection against meningococcal disease for travelers.

Vaccination Against Meningococcal Disease

Currently available vaccines to protect against meningococcal disease consist of two major classes, quadrivalent unconjugated polysaccharide vaccines (MPSV4) and quadrivalent polysaccharide-protein conjugate vaccines (MCV4). Although both types of vaccines provide protection against four serogroups, conjugate vaccines
of protection against meningococcal disease. The changeable nature of serogroup distribution presents a formidable challenge to effective traveler immunization. Although serogroups B and C are responsible for most cases of meningococcal disease in developed countries, serogroup distribution varies across geographic locations at any given time.\textsuperscript{14} For example, serogroup Y is increasing in the United States and Colombia, while serogroup C is increasing in Brazil and the Czech Republic, yet declining in the UK. Serogroup W-135 is prevalent in Argentina and South Africa.\textsuperscript{11,13,15–19}

Reduction in nasopharyngeal carriage and contribution toward herd immunity are also needed to reduce the risk of meningococcal transmission in many common contexts. Increased rates of carriage and transmission are observed among individuals living in close, crowded areas such as military barracks, university dormitories, or crowded houses, as well as those who travel to the Hajj—the annual pilgrimage to Mecca and Medina.\textsuperscript{20}

Another obstacle is the lack of a vaccine effective in infants and children <2 years of age. Currently, there is no broadly protective meningococcal (ACWY) vaccine licensed for use in infants or in young children <2 years of age. Although ACWY-D (Menactra, Sanofi Pasteur Inc., Swiftwater, PA, USA) has been approved in the United States and Canada for immunization of individuals aged 2 to 55 years and provides effective protection against meningococcal disease caused by the four serogroups,\textsuperscript{21,22} the vaccine does not elicit an adequate immune response in infants. Rapid waning of antibodies in children vaccinated at age 2 years also has been observed.\textsuperscript{23,24} The difference in immunogenicity profiles of the two vaccines may be due to differences in the dose and length of meningococcal oligosaccharides, specific conjugation chemistry, or the carrier protein utilized.\textsuperscript{21}

The multiserogroup profile of meningococcal disease and the unpredictability of serogroup distribution argues that effective control will require the greater widespread use of broadly immunogenic, broadly protective meningococcal vaccines. A conjugate vaccine that protects against multiple serogroups, reduces carriage, contributes to herd immunity, and elicits an immune response in infants and young children is required to improve current options for traveler immunization against meningococcal disease.

There are currently three multivalent polysaccharide vaccines available against groups A, C, Y, and W-135 combined: Menomune (MPSV4, Sanofi Pasteur Inc., Swiftwater, PA), Mencevax (GlaxoSmithKline, Australia), and ACWY Vax (GlaxoSmithKline, Middlesex, UK) (Table 2). Multiple monovalent, bivalent, and quadivalent conjugate meningococcal vaccines have also been developed. Of these, two provide multivalent protection against serogroups A, C, Y, and W-135: a meningococcal diphtheria toxoid vaccine (Menactra, Sanofi Pasteur Inc.), and, most recently, a CRM197 oligosaccharide conjugate vaccine (ACWY-CRM; Menveo, Novartis Vaccines and Diagnostics, Cambridge, UK).

### Table 1 Advantages of conjugate vaccines\textsuperscript{10}

<table>
<thead>
<tr>
<th>Property</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
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<tbody>
<tr>
<td>Effective in infants</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immune memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prolonged duration of protection</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Booster effect</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduction of carriage</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Contributes to herd effect</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyporesponsiveness with repeated dosing</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
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for meningococcal disease have several advantages over polysaccharide vaccines (Table 1).\textsuperscript{10}

Polysaccharide vaccines are safe and have good short-term immunogenicity in older children and adults.\textsuperscript{6} However, polysaccharide vaccines also have several limitations in terms of duration and wide applicability. Polysaccharide vaccines are known to have poor immunogenicity and lack of effectiveness in children less than 2 years of age.\textsuperscript{10} Their mechanism of action involves a T cell-independent response; therefore, they do not induce immunologic memory. There exists the potential to induce hyporesponsiveness with repeated doses, protection is of limited duration, usually 3 to 5 years, and they show little or no protection against nasopharyngeal carriage.\textsuperscript{6,10}

In contrast, the immune response to a conjugate meningococcal vaccine is T cell dependent, potentially increasing antibody levels and serum bactericidal activity (SBA) in all age groups, as well as inducing the formation of memory B cells. This population of long-lasting B cells allows the body to mount an anamnestic response after antigen reexposure.\textsuperscript{12} This provides a booster effect on subsequent vaccination or exposure and overcomes hyporesponsiveness. In addition, unlike polysaccharide meningococcal vaccines, conjugate vaccines have been shown to reduce nasopharyngeal carriage of \textit{N meningitidis} and, therefore, to reduce disease transmission and contribute to herd immunity in populations.\textsuperscript{10}

Although monovalent vaccines are not recommended for travelers, a successful meningococcal C (MenC) conjugate vaccination campaign in the UK has shown that conjugate vaccines are effective.\textsuperscript{13} In 1999, the UK became the first country to introduce a national immunization program for meningococcal serogroup C conjugate vaccines, which reduced disease by 86.7\% for targeted age groups (<20 y of age). Reductions in both the incidence of infection and fatalities have been observed since the introduction of the vaccines, as well as evidence of herd immunity in unvaccinated cohorts of the target age groups.\textsuperscript{13}

### Remaining Unmet Needs

There are several unmet needs hindering the goal of protection against meningococcal disease. The
Infants (<2 y) in phase II and phase III trials. In clinical studies, more individuals achieved a protective immune response [serum bactericidal assay using human complement (hSBA) titer ≥1:8 with ACWY-CRM] compared with MPSV4 and ACWY-D at 1 month postvaccination. As such, ACWY-CRM provides the potential for protection against meningococcal disease caused by serogroups A, C, W-135, and Y for the widest age range—from infants as young as 2 months to older adults.\(^{38,40,41}\)

**CRM\(^{197}\)**

ACWY-CRM has been developed using oligosaccharides linked to the carrier protein CRM\(^{197}\), a non-toxic mutant of diphtheria toxin. CRM\(^{197}\) has been shown to be useful as a protein carrier for several previously developed conjugate vaccines; it elicits a robust immune response in a broad range of age groups (including infants from 2 mo of age) and has a well-established safety profile.\(^{42}\) Studies have shown that vaccines incorporating CRM\(^{197}\) have contributed to significant declines in disease in countries implementing vaccination campaigns.\(^{43}\) CRM\(^{197}\) vaccines improve and prolong the immune response to bacterial polysaccharides by inducing high levels of bacterial antibodies with high avidity, including in young infants.\(^{44}\)

### Safety and Immunogenicity

#### Adults

In adults, the immune response to ACWY-CRM is at least as robust as to ACWY-D and is superior for certain serogroups.\(^{41}\) A comparison study of ACWY-CRM with ACWY-D enrolled 1,359 adults aged 19 to 55 years. One month after vaccination with ACWY-CRM, the percentage of subjects with hSBA titer ≥1:8 was 69% to 94%, comparable to results observed with ACWY-D for A and W serogroups (A: 69% vs 70% and W: 94% vs 90%, respectively), and superior for serogroups C (80% vs 72%, respectively) and Y (79% vs 70%, respectively) (lower limit of the two-sided 95% CI >0%) (Figure 1). Levels of hSBA GMTs were superior with ACWY-CRM compared with ACWY-D for all serogroups except A, for which they were comparable.\(^{41}\) Similar results were observed using the composite endpoint of seroresponse. Pain was the most frequently reported local reaction and headache the most frequent systemic reaction. The majority of local and systemic reactions were mild or moderate, and there were no significant differences between the two vaccines.\(^{41}\) Additionally, in multiple clinical trials, there have been no cases of Guillain–Barré syndrome observed with ACWY-CRM.

Studies are currently ongoing to assess immunogenicity and safety of ACWY-CRM in older adults aged 55 to 65.

#### Adolescents

Vaccination with ACWY-CRM results in a protective immune response in adolescents (aged 11–18 y), which is comparable to that observed with MPSV4 and ACWY-D and is statistically significantly different for certain serogroups.\(^{40,45}\) A phase II multicenter US study in adolescents (aged 11–17 y) reported significantly greater immunogenicity at 1 month postvaccination with ACWY-CRM compared with MPSV4. Significantly more subjects achieved hSBA titer ≥1:8 after 1 month with ACWY-CRM compared with MPSV4 for serogroups A, C, and Y (\(p < 0.001\); Figure 2). By 12 months, significantly more adolescents were protected against serogroups C, W-135, and Y with ACWY-CRM (\(p < 0.01\)). Levels of hSBA GMTs remained significantly higher with ACWY-CRM for serogroups W-135 and Y (\(p < 0.001\)) and were comparable between vaccines for A and C.\(^{45}\)

In the subsequent phase III study in 2,170 adolescents (aged 11–18 y), the percentage of subjects with a postvaccination hSBA titer ≥1:8 with ACWY-CRM was superior compared with the response to ACWY-D for serogroups A, W-135, and Y and was noninferior for serogroup C (lower limit of the two-sided 95% CI >0%) (Figure 3).\(^{40}\) The level of hSBA GMTs was significantly lower than that observed with ACWY-D for serogroups A and C.\(^{40}\)
higher with ACWY-CRM versus ACWY-D for all four serogroups. The percentage of seroresponders was significantly higher for ACWY-CRM (68%–75%) than for ACWY-D (41%–66%) for serogroups A, W-135, and Y, and comparable for serogroup C (75% vs 73%, respectively). Immune response was found to persist at 22 months, with a statistically significantly higher \((p < 0.05)\) proportion of subjects achieving hSBA titer \(\geq 1:8\) in the ACWY-CRM group compared with the ACWY-D group for serogroups A, W-135, and Y.\(^4\)

Overall, tolerability was comparable among the vaccines. Pain at injection site was the most common local reaction in both studies, reported by 44% to 56% of subjects; with no difference between groups. The most common systemic reaction in both studies was headache.\(^4^0,4^5\) Significantly more adolescents reported nausea with ACWY-CRM compared with MPSV4 \((p = 0.009);\) no other significant difference in adverse effects was noted.\(^4^5\)

**Children, Aged 2 to 10 Years**

In children (aged 2–10 y), a single-center, phase II US study \((N = 619)\) reported a superior protective immune response with ACWY-CRM compared with MPSV4 for all four serogroups at 1 and 12 months.\(^4^7\) One month after administration, 73% to 92% of children...
Figure 3 Percentage of adolescents with hSBA titers $\geq 1:8$ at 1 month postvaccination with ACWY-CRM vs ACWY-D.\textsuperscript{40}

in the ACWY-CRM group had an hSBA titer $\geq 1:8$ for all serogroups versus 37% to 65% for MPSV4. This superior antibody response was maintained at 12 months for serogroups A, W-135, and Y (Figure 4).\textsuperscript{47}

Similarly, hSBA GMTs were significantly higher across serogroups 1 month after vaccination with ACWY-CRM ($p < 0.01$) and remained significantly higher at 12 months for all serogroups except C.\textsuperscript{47}

More children vaccinated with ACWY-CRM experienced local and systemic reactions compared with those vaccinated with MPSV4; rates of pain (32% vs 24%), erythema (16% vs 6%), and induration (14% vs 4%) were significantly higher with ACWY-CRM compared with MPSV4, respectively ($p < 0.05$). Most local reactions were mild or moderate, and there was no significant difference between vaccines in severe systemic reactions.\textsuperscript{47}

Infants

Infants experience the highest incidence of invasive meningococcal disease (9.2/100,000 population)\textsuperscript{3} and the highest mortality rate (0.95/100,000 population) (1990–2002).\textsuperscript{4,16,48} In three published studies in infants and toddlers to date, ACWY-CRM has been well tolerated and has resulted in a protective immune response in this age group.\textsuperscript{37–39}

In phase II studies in infants, ACWY-CRM was studied using two or three doses as well as with or
without adjuvant; similar immunogenicity was observed whether or not adjuvant was present. In a randomized, open-label, controlled study in 2-month-old UK infants ($n = 225$) and Canadian infants ($n = 196$), $\geq 88\%$ achieved hSBA titer $\geq 1:8$ in the three-dose (2,3,4 mo) UK group. A second randomized phase II study evaluated 180 infants in the UK and Canada vaccinated with ACWY-CRM at age 2 and 4 months. At age 5 months, 70% to 89% of infants had hSBA titer $\geq 1:8$ for all serogroups except A (44% to 49%). Finally, a phase II study evaluating ACWY-CRM in infants and toddlers ($N = 175$) aged 6 and 12 months showed that after a second dose at 12 months of age, hSBA $\geq 1:8$ was achieved by 83% of infants against serogroup A and by 100% of infants against serogroups C, W, and Y. Overall, erythema and irritability were the most common adverse events and most local reactions were mild or moderate.

Concomitant Administration

A study in 1620 adolescents (aged 11–18 y) has shown that ACWY-CRM can be administered concomitantly with the tetanus-diphtheria-acellular pertussis booster (Tdap; Boostrix; GlaxoSmithKline, Research Triangle Park, NC, USA) and human papillomavirus vaccines (HPV; Gardasil; Merck and Co. Inc., Whitehouse Station, NJ, USA) without decreased immunogenicity. The only significant difference in immune response to Tdap antigens was in the ACWY-CRM–Tdap group, which experienced an enhanced response to the pertussis antigens. Seroconversion rates for HPV were $>98\%$ for all HPV types in each group. Concomitant administration of the HPV vaccine with ACWY-CRM and Tdap did not increase reactogenicity.

Conclusion

Due to the considerable and unpredictable variation of serogroup distribution globally, routine meningococcal disease vaccination in the traveler’s home country, particularly monovalent vaccines such as MenC in the UK, will not ensure protection at his or her destination. Broad, durable protection provided by immunization with a quadrivalent conjugate vaccine is more advantageous for travelers who may be exposed to serogroups that are not endemic to their home country or region. Of the available conjugate vaccines, ACWY-D can be given to children as young as age 2 years and is recommended for vaccination of travelers. A new vaccine recently developed using the CRM$^{197}$ carrier protein may provide additional options for protection of young infants through adults. Although currently indicated for use in adolescents and adults age 11 to 55 years, ACWY-CRM has proven immunogenic in all age groups, including infants (≥2 months of age), toddlers, children, adolescents, and adults, and has the potential to provide broad protection to the widest age range of individuals.

Meningococcal vaccination has the potential to greatly reduce meningococcal morbidity and mortality. Current meningococcal vaccines are effective but have limitations. New conjugate and protein vaccines in development have the potential to protect all critical age groups against all clinically important meningococcal serogroups.

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Declaration of Interests

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