Conjugated vaccines against serogroup A, C, W-135 and Y disease

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Review the current evidence on available and candidate quadrivalent meningococcal conjugate vaccines.

Methods: A comprehensive overview of data on the currently available A-C-W135-Y meningococcal vaccine and the results of late stage development of novel quadrivalent candidate vaccines were reviewed. Conclusions: Licensure of highly effective meningococcal C conjugate vaccines represented an enormous progress in the possibility of controlling meningococcal C disease. The unpredictable changing serogroup epidemiology of meningococcal disease emphasizes the need of developing combination conjugate vaccines, containing more than one meningococcal polysaccharide, to broaden protection against the disease. A quadrivalent meningococcal vaccine (A-C-W135-Y) conjugated to diphtheria toxoid is available only in United States and Canada for use in persons 2-55 years of age. However, in infants (the age group with the highest incidence rates of disease) the vaccine proved to be not immunogenic and is therefore not licensed for use in children younger than 2 years. A novel tetravalent meningococcal vaccine (A-C-W135-Y) conjugated to a non-toxic diptheria mutant toxin (CRM-197) is being evaluated in Phase III trials and has demonstrated to be immunogenic and well tolerated in all age groups, including infants, representing, at last, a real possibility of a broader protection against meningococcal disease.

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

The polysaccharide vaccines currently available offer protection against serogroups A, C, W135 and Y. These vaccines proved to be safe and effective in controlling outbreaks and epidemics. However, in common with other unconjugated polysaccharide vaccines, do not generate adequate immune response in children under 2 years of age because of the lack of response to T-independent antigens at this age. Another important characteristic of these vaccines is that, even in patients over 2 years of age, the protection offered is of limited duration; they are unable to induce immune memory. Furthermore, they are capable of inducing hyporresponsiveness after subsequent doses (1,2).

The conjugation of polysaccharides to protein carriers (non-toxic diphtheria mutant toxin [CRM197] or tetanus toxoid) alters the nature of the antipolysaccharide response to a T-dependent response. When B cells recognize the polysaccharide they process the conjugated carrier protein and present peptide epitopes to T-CD4+ cells. This antigenic complex induces the production of elevated antibody levels, including in young infants, higher antibody avidity and increases serum bactericidal activity. They also induce the formation of long-lasting memory B lymphocyte populations, providing an excellent amnestic response (booster effect) on re-exposure (1,2).

Monovalent conjugated meningococcal vaccines were developed from meningococcal serogroup C isolates containing the polysaccharide capsule conjugated to the mutant diphtheria toxin or to the tetanus toxoid. After licensure, serogroup C meningococcal conjugate vaccines have been successfully introduced in UK, Spain and other European countries, Australia and Canada. All these countries observed a significant reduction in the incidence of meningococcal disease. A striking feature of these meningococcal C conjugate vaccination programs, that included catch-up of children and adolescents using different immunization strategies, has been the additional decrease in disease incidence in unvaccinated individuals as a result of herd immunity(2).

Serogroup distribution varies globally, regionally and over time. Due to this dynamic and unpredictable nature of the meningococcus epidemiology, combination conjugate vaccines, containing more than one meningococcal polysaccharide, have been developed to broaden protection against the disease. A quadrivalent meningococcal vaccine, A, C, Y and W-135, conjugated to diphtheria toxoid – (MCV4; Menactra™–sanofi-aventis)(3-5) was licensed on the basis of findings demonstrating noninferiority, in terms of immunogenicity and safety, to meningococcal quadrivalent polysaccharide vaccine (MPSV4).

The criteria of demonstrating immunologic noninferiority of MCV4 to MPSV4 was achieved in studies conducted in three age groups: children 2 to 10 years of age, adolescents 11 to 18 years of age and adults 18 to 55 years of age. Induction of immune memory was also demonstrated in young children
vaccinated with MCV4 (3,4). However, in infants the vaccine proved to be poorly immunogenic (5).

The percentage of subjects reporting systemic adverse events was similar among persons aged 11–55 years, who received either vaccine. Local adverse reactions were more common among those persons aged 11–55 years who received MCV4 than among those who received MPSV4, but comparable to that reported after Td Vaccine for those aged 11–18 years or typhoid Vaccine for those aged 18–55 years (3,4). A possible association between Guillain-Barre’s syndrome (GBS) and receipt of MCV4 was reported in adolescents 11–19 years (1.25 excess cases of GBS per 1,000,000 doses distributed). Based on the known risk of meningococcal disease, CDC continues to recommend routine vaccination with MCV4.

However, persons with a history of GBS should not be vaccinated with MCV4 unless they are at elevated risk for meningococcal disease (3,4). Currently, in USA, this vaccine is routinely recommended by the Advisory Committee on Immunization Practices for all persons aged 11 to 18 years and for high-risk groups. This vaccine is licensed in USA and Canada only for children from 2 years of age (3,4).

A novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM), developed by Novartis, is being evaluated in Phase III trials. Instead of diphtheria toxoid as the carrier protein, this vaccine uses CRM-197, a natural mutant of the diphtheria toxin. Studies have shown that the MenACWY-CRM vaccine is well tolerated and immunogenic in infants, toddlers and adolescents, offering the possibility to broad protection against meningococcal disease in all age groups (6-9). When compared with currently licensed quadrivalent meningococcal polysaccharide vaccine, Men ACWY-CRM vaccine induced greater immunogenicity for all serogroups. In a Phase III trial in which MenACWY-CRM was compared to MCV4, geometric mean titers were higher after MenACWY-CRM than MCV4 administration (9). When administered either as a 2- or 3-dose primary immunization schedule in infancy, MenACWY-CRM proved to be immunogenic against all serogroups.

Recent data showing that infants vaccinated with a nonadjuvanted formulation of the MenACWYCRM vaccine had only marginally lower rates of seroprotection compared with infants who received the adjuvanted MenACWYCRM vaccine suggest that the inclusion of an aluminum adjuvant to this MenACWY-CRM vaccine may be unnecessary (8). This nonadjuvanted formulation of the MenACWYCRM vaccine is now being further studied as the final formulation by the manufacturer.

In conclusion, meningococcal C conjugate vaccines proved to be highly effective, with a dramatic reduction in the incidence of meningococcal disease caused by serogroup C in countries that have introduced them in their mass immunization programs. MCV4, currently available in North America, is licensed only for children from 2 years of age. A novel quadrivalent meningococcal vaccine conjugated to CRM-197, currently being evaluated in Phase III trials is expected to be licensed for all age groups, based on recent results (6-9), at last providing a real possibility of a broad protection against meningococcal disease in infancy.

References


3. Notice to Readers: Recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of quadrivalent meningococcal conjugate vaccine (MCV4) in children aged 2 to 10 years at increased risk for invasive meningococcal disease. MMWR Wkly. 2007;56:1265–6


6. Jackson L, Jacobson R, Reisinger K et al. Immunogenicity At 12 Months Post-Vaccination With Novartis Vaccines’ Tetravalent Glycoconjugate Meningococcal ACWY Vaccine In Adolescents. Presented at: Infectious Diseases Society of America 45th Annual Meeting; October 4-7, 2007; San Diego, California, USA.

