Antibody Persistence and Booster Response of a Quadrivalent Meningococcal Conjugate Vaccine in Adolescents

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Objective To evaluate the tolerability and immunogenicity of a booster dose of the quadrivalent meningococcal conjugate vaccine MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics, Siena, Italy) administered 3 years after primary vaccination of adolescents enrolled in a phase 3 study with either MenACWY-CRM or MenACWY-D (Menactra, Sanofi Pasteur, Swiftwater, Pennsylvania).

Study design A total of 730 healthy adolescents participated, including 622 initial study participants who received primary vaccination with MenACWY-CRM (n = 367) or MenACWY-D (n = 255) 3 years previously and 108 age-matched vaccine-naïve controls. A subset of MenACWY-CRM (n = 83) and MenACWY-D (n = 77) recipients were administered a MenACWY-CRM booster dose 3 years postprimary vaccination. Immunogenicity prior to and after the booster dose of MenACWY-CRM was measured by serum bactericidal assay with human complement (hSBA). Local and systemic reactions and adverse events were monitored in subjects receiving the booster dose.

Results At 3 years postprimary vaccination, 64%, 82%, and 65% of subjects initially vaccinated with MenACWY-CRM (n = 367) showed hSBA titers ≥8 against serogroups C, W-135, and Y, respectively; this was lower for serogroup A (28%). Significantly more MenACWY-CRM recipients had hSBA titers ≥8 for serogroups W-135 and Y than MenACWY-D recipients (n = 255). A MenACWY-CRM booster dose resulted in 99%-100% of subjects demonstrating hSBA titers ≥8 against all serogroups, irrespective of primary vaccination (MenACWY-CRM, n = 83; MenACWY-D, n = 77). The booster dose was well tolerated without significant adverse events.

Conclusions MenACWY-CRM can be used to boost adolescents who have received a primary vaccination with either MenACWY-CRM or MenACWY-D. *(J Pediatr 2014;164:1409-15)*.

Neisseria meningitidis is a significant cause of meningitis and septicemia worldwide, with approximately 500 000 cases per year globally.[1] Although disease burden is greatest in infancy, mortality rates can be twice as high for adolescents and young adults than for the general population.[2-4] The elevated incidence seen in adolescence and young adulthood in many parts of the world probably is related to increased transmission through social activities,[4] and through living in close quarters, such as college dormitories and military barracks.[5]

Globally, 6 immunologically distinct serogroups (A, B, C, W-135, X, and Y) cause most meningococcal disease.[6] Recent surveillance data from the US demonstrated that the majority of cases of meningococcal disease in adolescents in the US are caused by serogroups C (39%), B (29%), and Y (27%).[7] However, there is considerable variation by geographical region and over time in the distribution of serogroups causing meningococcal disease.[6]

Two quadrivalent meningococcal conjugate vaccines have been licensed in the US for the prevention of meningococcal disease caused by serogroups A, C, W-135, and Y: MenACWY-CRM (Menveo, Novartis Vaccines and Diagnostics, Siena, Italy) licensed for ≥2 months to 55 years of age and MenACWY-D, (Menactra, Sanofi Pasteur, Swiftwater, Pennsylvania) licensed for ≥9 months to 55 years. Routine vaccination with a meningococcal conjugate vaccine for children aged 11-12 years has been recommended in the US since 2005. In January 2011, the US Advisory Committee on Immunization Practices recommended a booster dose at 16-18 years of age, based on data suggesting that antibody persistence wanes prior to the period of increased disease incidence in late adolescence.[8] In Europe, MenACWY-CRM and MenACWY-D are licensed for use in persons from 2 years of age, with no upper age limit.

MenACWY-CRM is comprised of capsular polysaccharides from serogroups A, C, W-135, and Y conjugated to a nontoxic mutant of diphtheria toxin—CRM_{197}. MenACWY-CRM has been shown to be immunogenic and well tolerated across all age groups, including infants aged 2-23 months,[9] children aged 2-10 years,[10] adolescents aged 11-18 years,[11] adults aged 19-55 years,[12] and adults aged 56-65 years.[13]

AE	Adverse event
GMT	Geometric mean titer
hSBA	Serum bactericidal assay with human complement
PP	Per-protocol
rSBA	Serum bactericidal assay with rabbit complement

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The initial study (Novartis study V59P13) was a randomized, multicenter, phase 3 study to compare the safety and immunogenicity of MenACWY-CRM and MenACWY-D in healthy subjects aged 11-55 years, with data in adolescents (11-18 years), and adults (19-55 years) reported separately.[11,12] In adolescents (n = 2170), a statistically significantly greater percentage of subjects achieved a seroresponse (serum bactericidal assay with human complement [hSBA] titers ≥8) 1 month following a single dose of MenACWY-CRM vs MenACWY-D for serogroups A, W, and Y (75% vs 67%, 96% vs 88%, 88% vs 69%, respectively) and MenACWY-CRM was noninferior to MenACWY-D for serogroup C (84% vs 84%).[11] In a follow-up study in a subgroup of subjects conducted at 21 months, immune responses persisted in both groups. As in the initial study, hSBA titers ≥8 for serogroups A, W-135, and Y were observed in significantly more subjects who had received MenACWY-CRM compared with those who had received MenACWY-D (36% vs 25%, 84% vs 74%, 67% vs 54%, respectively) with similar values for serogroup C (62% vs 58%).[14]

The current study was conducted to evaluate further antibody persistence in adolescents who received MenACWY-CRM or MenACWY-D, 3 years after primary vaccination. Furthermore, the immunogenicity and tolerability of a booster dose of MenACWY-CRM in a subset of subjects who had received MenACWY-CRM or MenACWY-D was assessed. A vaccine naïve control group was also enrolled to evaluate background rates of bactericidal antibodies.

Methods

Details of the parent study and the 21-month persistence study have been published previously.[11,14] Ethics review committees of participating centers approved the study protocol. Subjects who had participated in the initial study at age 11-18 years were invited to participate in the extension persistence study, starting 21 months after the completion of the initial study and were requested to continue in further persistence evaluations. The criterion for inclusion was the availability of an hSBA result for at least 1 serogroup 1 month after primary vaccination in the initial study.

Subjects enrolled to receive a booster dose in this study were recruited from subjects in the initial study who had not already been enrolled in the 21-month persistence study, where possible, to permit the possibility of ongoing persistence evaluations. As needed, subjects were randomly selected from the persistence groups to be switched to the booster groups to achieve the necessary enrollment.

In addition, age-matched healthy meningococcal vaccine-naïve subjects were recruited. Written, informed consent was obtained from all subjects, or their legal guardian, before enrollment into the study.

Subjects were divided into 5 groups: groups I and II were study subjects who had received MenACWY-CRM or MenACWY-D, respectively, in the initial study and were enrolled for persistence analysis; group III comprised newly enrolled vaccine-naïve age-matched (control) subjects; and groups IV and V were study subjects who had previously received MenACWY-CRM or MenACWY-D, respectively, and subsequently received a booster dose of MenACWY-CRM 3 years after the initial vaccination (**Figure 1**; available at www.jpeds.com).

Serum samples were taken on day 1 of this study, to determine bactericidal antibody persistence or, with the naïve group, the background prevalence of bactericidal antibodies. Groups I and II received no further study vaccinations, in view of planned future persistence assessments. Subjects in groups IV and V both received a single booster vaccination with MenACWY-CRM and were evaluated both pre- and postvaccination 28 days later.

Subjects in groups IV and V received MenACWY-CRM. This vaccine comprises 2 components—10 μg lyophilized serogroup A capsular polysaccharide conjugated to CRM_{197}, which was reconstituted immediately before administration in 0.5 mL injection volume using a solution containing 5 μg each of the capsular polysaccharides of serogroups C, W-135, and Y conjugated to CRM_{197}. The reconstituted vaccine was administered by intramuscular injection into the anterolateral area of the left deltoid.

Immunogenicity Assessments

Immunogenicity was assessed as the percentage of subjects with reciprocal hSBA titers ≥8 against each serogroup, as previously described.[15] In addition, samples from subsets of subjects (100 from each of groups I and II, 50 from group III and all subjects in groups IV and V) were analyzed using a serum bactericidal antibody analysis using rabbit complement (serum bactericidal assay with rabbit complement [rSBA]) with similar methods.[15] The laboratory staff who performed the hSBA and rSBA analyses were blinded to study vaccine and control group status.

Safety Assessment

The safety and tolerability of a booster dose of MenACWY-CRM was assessed in subjects in groups IV and V. The incidence of solicited local and systemic adverse events (AEs) and any other AEs occurring up to 7 days after the booster dose were collected. Medically attended AEs were recorded between days 8 and 28. AEs were judged by the investigator as to whether they were at-least-possibly-related to study vaccine. In addition, the onset of new chronic diseases in the period since the end of the initial study was recorded for subjects who participated in the initial study (groups I, II, IV, and V).

Erythema and induration were classified as severe if >50 mm; fever was classified as severe if ≥40°C. All other reactions, including local pain, were classified as mild (transient with no limitation on normal daily activities), moderate (some limitation in normal daily activities), or severe (unable to perform normal daily activities).

Statistical Analyses

The primary objective of this study was to evaluate immunogenicity—the percentage of subjects with hSBA titers ≥8 against each of the 4 serogroups 3 years after vaccination with MenACWY-CRM and MenACWY-D (groups I and