Phase III Comparison of an Investigational Quadrivalent Meningococcal Conjugate Vaccine with the Licensed Meningococcal ACWY Conjugate Vaccine in Adolescents

Lisa A. Jackson,1 Roger Baxter,2 Keith Reisinger,3 Annette Karsten,4 Jina Shah,4 Lisa Bedell,4 Peter M. Dull,4 and the V59P13 Study Group

1Group Health Center for Health Studies, Seattle, Washington; 2Kaiser Permanente Vaccine Study Center, Oakland, California; 3Primary Physicians Research, Pittsburgh, Pennsylvania; 4Novartis Vaccines & Diagnostics, Cambridge, Massachusetts; and 5Novartis Vaccines & Diagnostics, Marburg, Germany

Background. Neisseria meningitidis is an important cause of invasive bacterial infection in the United States, and disease rates are higher for adolescents than for the general population. Quadrivalent meningococcal conjugate vaccine is recommended for routine vaccination of adolescents and high-risk groups. This study compares the safety and immunogenicity of the Novartis Vaccines investigational quadrivalent meningococcal CRM197 conjugate vaccine, MenACWY-CRM, with the licensed meningococcal conjugate vaccine, Menactra.

Methods. In this multicenter phase III study, 2180 adolescents 11–18 years of age were randomly assigned to 4 groups (1:1:1:1) to receive a single dose of 1 of 3 lots of MenACWY-CRM or a single dose of Menactra. Serum samples obtained before vaccination and 1 month after vaccination were tested for serogroup-specific serum bactericidal activity using human complement (hSBA). The hSBA titers after vaccination with MenACWY-CRM or Menactra were compared in noninferiority and superiority analyses.

Results. The hSBA geometric mean titers after MenACWY-CRM vaccination were higher than the hSBA geometric mean titers after Menactra vaccination, and criteria for superiority were met for this end point for all 4 serogroups. Also, the criteria for superiority of MenACWY-CRM, compared with Menactra, were met for the end points of proportion of subjects with postvaccination hSBA titers ≥1:8 and proportion of seroresponders for serogroups A, W-135, and Y. MenACWY-CRM was noninferior to Menactra for serogroup C for these end points. Reactogenicity was similar, with 64% of the MenACWY-CRM recipients and 70% of the Menactra recipients reporting mild and/or moderate solicited reactions. Neither vaccine was associated with a serious adverse event.

Conclusions. MenACWY-CRM vaccine is well tolerated in adolescents and generates a stronger immune response than Menactra for all 4 serogroups.

has been available since 1981 and has been used selectively for individuals at increased risk for meningococcal disease. In January 2005, a quadrivalent meningococcal polysaccharide-protein conjugate vaccine (Menactra; Sanofi Pasteur), which contains saccharides derived from the capsules of *N. meningitidis* conjugated to denatured diphtheria toxoid carrier proteins, was licensed by the US Food and Drug Administration. In the United States, this vaccine is currently recommended for all persons 11–18 years of age and all persons 2–55 years of age who are at increased risk for meningococcal disease [4].

Meningococcal conjugate vaccines offer several important advantages over unconjugated meningococcal polysaccharide vaccines. Unconjugated meningococcal polysaccharide vaccines induce a largely T cell–independent response and therefore do not confer long-lasting immunity [5]. Although the duration of immunity to the relatively recently introduced meningococcal conjugate vaccines is not well defined, conjugate vaccines induce a T cell–dependent response, can induce immunologic memory, and are believed to be associated with longer-lasting immunity. Furthermore, meningococcal conjugate vaccines reduce asymptomatic carriage of *N. meningitidis* [6], and this reduction can lead to herd immunity, as has been demonstrated in the United Kingdom since introduction of the monovalent meningococcal C conjugate vaccines into the routine childhood vaccination schedule [7]. In the United Kingdom, the vaccine effectiveness of meningococcal C conjugate vaccines has been shown to persist for ≥4 years in persons vaccinated at ≥3 years of age [8]. Lastly, unconjugated meningococcal polysaccharide vaccines have been demonstrated to induce antibody hyporesponsiveness to subsequent doses of unconjugated or conjugated meningococcal vaccines [9–12]; this antibody hyporesponsiveness may occur because of depletion of polysaccharide-specific memory B cells as a result of repeated exposure to unconjugated polysaccharide [13]. In contrast, meningococcal conjugate vaccines do not induce antibody hyporesponsiveness to subsequent vaccinations [11].

To expand the number of options for prevention of meningococcal disease in children and adults, a quadrivalent meningococcal conjugate vaccine (MenACWY-CRM; Novartis Vaccines) has been developed that includes CRM197, a naturally occurring nontoxic mutant of diphtheria toxin, as the carrier protein [14]. Previous studies have found that this vaccine is well tolerated and immunogenic in infants [15, 16] and children [17] and elicits a noninferior immune response, compared with unconjugated meningococcal polysaccharide vaccine, in adolescents [18]. We report here the results of a phase III randomized trial of the safety and immunogenicity of MenACWY-CRM, compared with the safety and immunogenicity of the currently licensed quadrivalent meningococcal conjugate vaccine, Menactra, in healthy adolescents 11–18 years of age. This is the first direct comparison of these vaccines.

## METHODS

### Study design.

The objectives of this Phase III randomized, observer-blind trial were to compare the safety and immunogenicity of MenACWY-CRM with those of Menactra in healthy subjects 11–55 years of age and to assess the consistency of the immune response to 3 lots of MenACWY-CRM in healthy subjects 11–18 years of age. This article reports the results of the safety and immunologic evaluations in 2170 subjects 11–18 years of age; the data on subjects 19–55 years of age will be reported separately.

Subjects who were enrolled at 44 clinical centers in the United States were randomly allocated 1:1:1:1 to 1 of 4 groups (MenACWY-CRM Lot 1, Lot 2, or Lot 3, or Menactra). Randomization was implemented using 4-subject blocks and stratified by center via an interactive voice response system provided by an external vendor. An unblinded member of the study-site staff telephoned the interactive voice response system and, on the basis of the age of the subject (adult or adolescent) and the site, the interactive voice response system assigned a subject number and treatment group. Subject exclusion criteria included household contact with or intimate exposure to an individual with *N. meningitidis* infection in the 60 days prior to enrollment; previous vaccination with a meningococcal vaccine; receipt of any vaccine within 1 month prior to enrollment; serious acute or chronic illness; or history of hypersensitivity to any vaccine component. Written informed consent was obtained from all subjects and from the parents or legal guardians of adolescents 11–17 years of age.

**Study vaccines.** Each dose of study vaccine (MenACWY-CRM) consisted of 2 components—the first containing 10 μg of lyophilized meningococcal serogroup A capsule polysaccharide conjugated to CRM197 (MenA) and the second con-

### Table 1. Baseline characteristics of enrolled population.

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>MenACWY-CRM (n = 1640)</th>
<th>Menactra (n = 540)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>14.2 ± 2.2</td>
<td>14.1 ± 2.2</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Race or ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Black</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>White</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Weight, mean kg ± SD</td>
<td>61.0 ± 18.9</td>
<td>60.1 ± 18.6</td>
</tr>
<tr>
<td>Height, mean cm ± SD</td>
<td>163.0 ± 12.0</td>
<td>162.5 ± 11.8</td>
</tr>
</tbody>
</table>

**NOTE.** SD, standard deviation.
MenACWY-CRM Vaccine in Adolescents

CID 2009:49 (1 July) e3

Figure 1. Subject disposition flowchart

- Figure 1: Subject disposition flowchart

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3

- MenACWY-CRM Vaccine in Adolescents

- CID 2009:49 (1 July) e3
Figure 2. Solicited (A) local and (B) systemic reactions up to 7 days after vaccination for all subjects.

- Mild, no limitation in normal daily activity; moderate, some limitation in normal daily activity; severe, unable to perform normal daily activity because of the reaction.
- Mild, \( \leq 25 \text{ mm} \); moderate, 26–50 mm; severe, \( >50 \text{ mm} \).
- Mild, 38.0°C–38.9°C; moderate, 39.0°C–39.9°C; severe, \( \geq 40°C \).

ratio of the postvaccination GMTs was within the 2-sided 95% confidence interval (CI) of 0.5–2.0. GMTs were constructed by exponentiation (base 10) of the least square means of the logarithmically transformed (base 10) titers, and their 95% CIs were obtained from an analysis of variance model, with vaccination group and center as factors in the model.

For comparisons of the immunogenicity of MenACWY-CRM (predefined as all 3 lots combined) and Menactra, 3 immunologic end points were defined. For each serogroup, these end points comprised the postvaccination hSBA GMTs, the proportion of subjects with a postvaccination hSBA titer \( \geq 1:8 \), and the proportion of seroresponders.

Seroresponse was a composite end point defined by an increase in hSBA titer from before to after vaccination. If the prevaccination titer was below the limit of detection (\( <1:4 \)), seroresponse was defined by seroconversion to a postvaccination titer of \( \geq 1:8 \). If the prevaccination titer was \( \geq 1:4 \), seroresponse was defined by a 4-fold or greater increase in titer from before to after vaccination.

The criteria defining noninferiority and statistical superiority for each end point were prespecified in the study protocol. For the GMT end point, the immunogenicity of MenACWY-CRM was considered to be noninferior to the immunogenicity of Menactra if the lower limit of the 2-sided 95% CI around the ratio of the GMTs was \( >0.5 \); superiority was defined as a lower limit of \( >1 \). For the end points of proportion of subjects with a postvaccination hSBA titer \( \geq 1:8 \) and the proportion of seroresponders, the 2-sided 95% CI for the difference in proportions (MenACWY-CRM minus Menactra) was first determined. Noninferiority was then defined by a lower limit of the 2-sided 95% CI of greater than \(-10\%\) , and superiority was defined as a lower limit of \( >0\% \).

Because of the limited availability of qualified human complement, hSBA titers were not assessed for all serogroups for all subjects in the immunogenicity evaluation subsets. Instead, the number of specimens randomly selected for testing for hSBA titers in each serogroup was determined on the basis of the variance in serogroup-specific hSBA titers observed in a previous phase II MenACWY-CRM study. Because the highest variance was seen for serogroup C, a greater number of samples were selected for testing for this serogroup. The third-party interactive voice response system randomization vendor performed the random selection of specimens to be tested.

The immunogenicity analyses were based on the per protocol population data set. To be included in the per protocol data set, subjects needed to receive the correct vaccination, to have an evaluable titer both before and after vaccination, and to not have any major protocol deviations.

RESULTS

A total of 2180 subjects 11–18 years of age were enrolled and randomly assigned to groups, and 2170 received 1 dose of either MenACWY-CRM (\( n = 1631 \)) or Menactra (\( n = 539 \)). The 10 subjects who were not vaccinated were excluded because of withdrawal of consent (\( n = 5 \)); inappropriate enrollment—that is, they no longer satisfied the entry criteria (\( n = 4 \)); or inability to supply a blood sample (\( n = 1 \)). The demographic characteristics for enrolled subjects were similar between the MenACWY-CRM and Menactra groups (table 1). Of the 2180 subjects enrolled, 2118 (97%) completed the study (figure 1).

Safety Analysis

Solicited adverse events. Both vaccines were well tolerated, with comparable reactogenicity. Overall, the percentage of subjects who reported solicited local and systemic reactions was similar between MenACWY-CRM and Menactra recipients (fig-
Table 2. Comparison of serum bactericidal activity using human complement (hSBA) geometric mean titers (GMTs), percentages of subjects with an hSBA titer $\geq 1:8$ one month after vaccination with MenACWY-CRM or Menactra, and the results of noninferiority and superiority analyses.

<table>
<thead>
<tr>
<th>Serogroup, vaccine</th>
<th>No. of serum samples tested</th>
<th>GMT (95% CI)</th>
<th>Ratio of GMTs$^a$ (95% CI)</th>
<th>Noninferior$^b$</th>
<th>Superior$^c$</th>
<th>Percentage of hSBA titers $\geq 1:8$ (95% CI)</th>
<th>Group difference$^d$ (95% CI)</th>
<th>Noninferior$^b$</th>
<th>Superior$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.63 (1.31 to 2.02)</td>
<td>Yes</td>
<td>Yes</td>
<td>75 (73 to 78)</td>
<td>Yes</td>
<td>8 (3 to 14)</td>
<td>67 (62 to 72)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>1075</td>
<td>29 (24 to 35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menactra</td>
<td>359</td>
<td>18 (14 to 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.27 (1.01 to 1.60)</td>
<td>Yes</td>
<td>Yes</td>
<td>84 (82 to 88)</td>
<td>No</td>
<td>1 (–3 to 5)$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>1483</td>
<td>59 (48 to 73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menactra</td>
<td>501</td>
<td>47 (36 to 61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W-135</td>
<td>2.00 (1.66 to 2.42)</td>
<td>Yes</td>
<td>Yes</td>
<td>96 (95 to 97)</td>
<td>Yes</td>
<td>8 (4 to 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>1024</td>
<td>87 (74 to 102)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menactra</td>
<td>288</td>
<td>44 (35 to 54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>2.92 (2.26 to 3.52)</td>
<td>Yes</td>
<td>Yes</td>
<td>88 (85 to 90)</td>
<td>Yes</td>
<td>19 (14 to 25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>1036</td>
<td>51 (42 to 61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menactra</td>
<td>294</td>
<td>18 (14 to 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval.

$^a$ Ratio of value for MenACWY-CRM to value for Menactra.

$^b$ Noninferiority was determined if the lower limit of the 95% CI around the GMT ratio was $>0.5$ or if the lower limit of the 95% CI around the group difference was $>10$.

$^c$ Superiority was determined if the lower limit of the 95% CI around the GMT ratio was $>1$ or if the lower limit of the 95% CI around the group difference was $>0$.

$^d$ Value for MenACWY-CRM minus value for Menactra.

$^e$ Although both groups had a value of 84, there is a group difference of 1 because of rounding.

Immunogenicity

The prespecified criteria for lot-to-lot consistency (based on 95% CIs around the ratios of postvaccination GMTs being within the interval 0.5–2.0) were met for each pairwise comparison of the 3 lots of MenACWY-CRM vaccine. The 2-sided 95% CIs were 0.68–1.38 for serogroup A, 0.68–1.77 for serogroup C, 0.63–1.67 for serogroup W-135, and 0.61–1.5 for serogroup Y. Because there were no lot-to-lot differences, a comparison of the combined MenACWY-CRM cohort with Menactra vaccinees was possible.

In a comparison of the immunogenicity of MenACWY-CRM with that of Menactra, hSBA GMTs after vaccination with MenACWY-CRM were consistently higher than hSBA GMTs after vaccination with Menactra and met the prespecified criteria for superiority for all 4 serogroups (table 2). Clear differences are observed in the reverse cumulative distribution curves of postvaccination hSBA titers for serogroups A, W-135, and Y, with the largest difference observed for Y (figure 3). For the immunogenicity measure of the proportion of subjects with a postvaccination hSBA titer $\geq 1:8$, the criteria for statistical superiority of the response to MenACWY-CRM, compared with the response to Menactra, were met for serogroups A, W-135, and Y, and the criteria for noninferiority were met for serogroup C (table 2). The largest difference in the proportion of persons with a postvaccination titer $\geq 1:8$ was seen for serogroup Y (88% with an hSBA titer $\geq 1:8$ after vaccination with MenACWY-CRM, compared with 69% after vaccination with Menactra).
Similarly, for the end point of proportion of seroresponders, in analyses of all subjects, the response to MenACWY-CRM met statistical superiority criteria, compared with the response to Menactra, for serogroups A, W-135, and Y and was non-inferior for serogroup C (table 3). In analyses restricted to subjects who were seronegative (hSBA titer <1:4) at baseline, similar differences in the proportion of seroresponders to MenACWY-CRM and Menactra were observed, with higher proportions seroconverting for serogroups A, W-135, and Y with MenACWY-CRM than with Menactra.

For serogroups W-135 and Y, analyses of the end point of a postvaccination titer $\geq 1:8$ show smaller differences between the MenACWY-CRM and Menactra groups than analyses of the end point of seroresponse. For both end points, however, the differences between the groups met the criteria for non-inferiority and for superiority of MenACWY-CRM, compared with Menactra. The proportion of participants with baseline titers $\geq 1:4$ was greater for serogroups W-135 and Y than for serogroups A and C. Thus, comparisons of the static end point of postvaccination titer $\geq 1:8$ tend to underestimate the difference in immunogenicity between MenACWY-CRM and Menactra, and larger differences are seen in analyses of the end point of seroresponse, because these analyses account for pre-vaccination titer.

**Additional Analyses**

The serogroup-specific hSBA GMTs to each vaccine, as well as the pattern of differences in GMTs between the MenACWY-CRM and Menactra groups, did not vary significantly by sex, age (11–14 years of age vs. 15–18 years of age), or body mass index (data not shown). Participants were also asked to report whether they had received a tetanus-reduced dose diphtheria toxoid (Td) vaccine during the 5 years before enrollment and, if so, the date of the most recent vaccination. Analyses of the serogroup-specific GMTs did not detect statistically significant differences in response by time since prior Td vaccination (data not shown).

**DISCUSSION**

These results confirm that MenACWY-CRM is well tolerated and immunogenic in healthy adolescents 11–18 years of age. Moreover, the immune response, as measured by hSBA GMTs, met the criteria for statistical superiority after vaccination with
Table 3. Comparison of the percentages of seroresponders according to prevaccination status and the results of the noninferiority and superiority analyses.

<table>
<thead>
<tr>
<th>Serogroup, by prevaccination status (hSBA titer) and vaccine</th>
<th>No. of serum samples tested</th>
<th>Seroconversion or seroresponse, %</th>
<th>Group difference in (95% CI)</th>
<th>Noninferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Seronegative (&lt;1:4)</td>
<td>1039</td>
<td>75</td>
<td>9 (3 to 15)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>347</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive (≥1:4)</td>
<td>36</td>
<td>58</td>
<td>−8 (−35 to 24)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>12</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1075</td>
<td>75</td>
<td>8 (3 to 14)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>359</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C</strong> Seronegative (&lt;1:4)</td>
<td>977</td>
<td>79</td>
<td>0 (−5 to 6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>331</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive (≥1:4)</td>
<td>506</td>
<td>68</td>
<td>6 (−2 to 15)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>170</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1483</td>
<td>75</td>
<td>2 (−2 to 7)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>501</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>W-135</strong> Seronegative (&lt;1:4)</td>
<td>609</td>
<td>94</td>
<td>10 (5 to 17)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>180</td>
<td>83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive (≥1:4)</td>
<td>415</td>
<td>47</td>
<td>19 (9 to 28)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>108</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1024</td>
<td>75</td>
<td>12 (6 to 18)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>288</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Y</strong> Seronegative (&lt;1:4)</td>
<td>630</td>
<td>81</td>
<td>27 (19 to 35)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>176</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive (≥1:4)</td>
<td>406</td>
<td>47</td>
<td>25 (16 to 34)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>118</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1036</td>
<td>68</td>
<td>27 (20 to 33)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MenACWY-CRM</td>
<td>294</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Numbers required to test were based on analysis of variability of seroresponse to each serogroup in previous trials, combined with relevant power calculations. Noninferiority and/or superiority analyses were performed only for the overall population as predefined in the study protocol. CI, confidence interval; hSBA, serum bactericidal activity using human complement; NA, not applicable.

a Value for MenACWY-CRM minus value for Menactra.
b Noninferiority was determined if the lower limit of the 95% CI around the group difference was > (1/10).
c Superiority was determined if the lower limit of the 95% CI around the group difference was > 0; analysis of subjects with a prevaccination titer <1:4 at baseline was performed post hoc.
MenACWY-CRM vaccine, compared with after vaccination with the currently licensed standard, Menactra, for all 4 serogroups. Similarly, statistical superiority was demonstrated for MenACWY-CRM for the end points of the proportion of subjects with a postvaccination hSBA titer $\geq 1:8$ and the proportion of seroresponders for serogroups A, W-135, and Y. For those end points, the response to MenACWY-CRM met the criteria for noninferiority for serogroup C.

Immunogenicity using human complement has been shown to be a good predictor of vaccine efficacy [19, 20], and vaccines licensed on the basis of immunogenicity trials have proven effective in large scale vaccination campaigns in the United Kingdom, Canada, Spain, and elsewhere [21–23]. Whether the differences in immunogenicity to the 2 vaccines in this clinical trial translate to clinically significant differences in efficacy is uncertain.

The reasons for the higher hSBA response of adolescents to MenACWY-CRM, compared with the hSBA response of adolescents to Menactra, are unclear but are consistent with differences in immune responses to the 2 vaccines observed in other populations: in infants, Menactra administered in the first 6 months of life does not appear to stimulate adequate levels of immunity to serogroups C, W-135, or Y, as assessed by serum bactericidal activity assays using rabbit complement [24], whereas MenACWY-CRM formulations, with and without aluminum phosphate adjuvant, are immunogenic in this age group [15, 16]. The 2 vaccines have different carrier proteins, CRM$_{197}$ for MenACWY-CRM and diphtheria toxoid for Menactra. In addition, the techniques for generating oligosaccharides of pre-specified sizes and the selective conjugation chemistry that permits a consistent and well-characterized vaccine product with the MenACWY-CRM vaccine are all factors that could explain these differences in immune response [14].

A similar scenario has been observed with vaccines against Haemophilus influenzae type b disease (Hib). Although a Hib vaccine using diphtheria toxoid as the conjugate protein was initially demonstrated to be effective in a clinical trial in Finland [25], it had relatively limited immunogenicity in children <6 months of age [26, 27] and did not demonstrate efficacy in a clinical trial conducted among Alaska Native infants [28]. In contrast, a Hib vaccine using CRM$_{197}$ conjugate protein was shown to be immunogenic [27, 29] and efficacious in infants [30]. Alongside Hib vaccines using a tetanus toxoid protein or an outer membrane protein from N. meningitidis serogroup B, a Hib vaccine using CRM$_{197}$ conjugate protein has been used in the United States with subsequent near-elimination of invasive Hib disease [31, 32].

The epidemiology of meningococcal disease is highly variable, and rates of disease, as well as the serogroup distribution of cases, fluctuate by geographic region, by age group, and over time. This variability has been observed in the United States, where serogroup Y disease has increased dramatically over the past 20 years in terms of both absolute rate and proportion of cases of meningococcal disease [33, 34]. In the current study, the largest differences in immune response between the 2 vaccines were to serogroup Y, with GMTs of 51 after vaccination with MenACWY-CRM and of 18 after vaccination with Menactra. With regard to patients who lacked bactericidal antibodies at baseline, 81% of MenACWY-CRM recipients, compared with 54% of Menactra recipients, achieved a serogroup Y hSBA titer of $\geq 1:8$. Although the clinical significance of the lower immune response to serogroup Y after vaccination with Menactra, compared with after vaccination with MenACWY-CRM, cannot be inferred directly from these data, protection against serogroup Y disease is particularly relevant in the current epidemiologic environment in the United States, where approximately one-third of all meningococcal disease is due to this serogroup.

The long-term persistence of the hSBA titers to the 4 vaccine serogroups after MenACWY-CRM vaccination is currently unknown, although studies to assess the persistence of immune response after vaccination with MenACWY-CRM in various age groups are either planned or ongoing. In this study, blood samples were obtained for measurement of hSBA titers only at 1 month after vaccination, so persistence of the immune response could not be compared between the 2 vaccines. In a prior study that compared MenACWY-CRM with unconjugated meningococcal polysaccharide vaccine in adolescents, we found that 12 months after vaccination with MenACWY-CRM, $\geq 77\%$ of adolescents 11–17 years of age still had an hSBA titer $\geq 1:8$ for serogroups C, W-135, and Y. This fact suggests a persistence of clinical protection against those serogroups for $\geq 1$ year [18].

Data from the United Kingdom about patients who have received conjugate MenC vaccination have shown that, although the persistence of antibodies in infants may require a boost in the second year of life [35], persons vaccinated later in life (at $\geq 10$ years of age) have antibody persistence against serogroup C $\geq 5$ years after vaccination [36]. In the study by Snape et al. [36], the age at conjugate MenC vaccination was associated with the immune response. Children vaccinated at 12–15 years of age had higher rSBA titers at 5 years after vaccination than did those vaccinated at 6–9 years of age. Whether this was attributable to a more robust or mature immune response at the time of vaccination, a slower decrease in antibody titers, or other factors (e.g., different nasopharyngeal carriage rates) is difficult to conclude. This will remain an important question as children vaccinated in the United States at 11 years of age become young adults, when they may enter environments of increased meningococcal disease risk, such as college or military service. The highly successful MenC vaccination program in the United Kingdom targeted age groups from infancy to early adulthood. The unsuitability of the currently available...
quadrivalent polysaccharide and conjugate vaccines for use in infants leaves a clear medical need that the MenACWY-CRM vaccine may fill.

In summary, in this randomized trial, we have shown that the MenACWY-CRM vaccine generates robust immune responses in adolescents against all 4 serogroups, with responses that are noninferior for serogroup C and that met statistical superiority criteria for serogroups A, W-135, and Y, compared with responses generated by Menactra. On the basis of these and previous results, the MenACWY-CRM vaccine has the potential to provide broad serogroup protection for people across a wide age range, including infants and toddlers, with a more favorable immune response in adolescents than that of the current licensed standard, Menactra.

Acknowledgments

Medical writing support was provided by Dr. Jonathan Brennan at Alphapharmax Healthcare Communications. Principal investigators were Martha Anderson, Wilson P. Andrews, Roger Baxter, Henry Bernstein, Stan Block, James Campbell, Ina Stephens, Shane Christensen, Blaise Congeni, Ashley Evans, Michael Gerber, Lisa Jackson, William Johnston, Henry Keyserling, Colin Marchant, Keith Reisinger, Edward Rothstein, Richard Rupp, Shelly Senders, and Ram Yoge.

Financial support. Novartis Vaccines.

Potential conflicts of interest. L.A.J. has received research funding from Novartis and Sanofi Pasteur and travel support from Novartis. R.B. has received research funding from Novartis and Sanofi Pasteur. K.R. has received grants and/or research funding from Novartis, Merck, Sanofi Pasteur, GlaxoSmithKline, Wyeth, and MedImmune and is a scientific advisor for Novartis and Merck. A.K., J.S., L.B., and P.M.D. are employees of Novartis Vaccines.

References