Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2–10 years of age

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ABSTRACT

Background: Routine administration of quadrivalent meningococcal conjugate vaccine to adolescents and certain high risk groups is recommended in the United States and Canada. We compared the immunogenicity and safety of an investigational quadrivalent meningococcal vaccine conjugated to CRM-197 (MenACWY-CRM) with a licensed quadrivalent vaccine conjugated to diphtheria toxoid (MCV4) in children aged 2–10 years.

Methods: Eligible 2–5-year-olds were randomized 1:2:2 to receive either 2 doses of MenACWY-CRM, or 1 dose of MenACWY-CRM or MCV4; 6–10-year-olds were randomized 1:1 to receive a single dose of MenACWY-CRM or MCV4. The primary immunogenicity assessment was seroresponse separately for the two age cohorts 28 days following a single dose of MenACWY-CRM or MCV4. Noninferiority and superiority criteria were predefined. Solicited injection-site and systemic reactions were collected for the 7 days postvaccination.

Results: A total of 2907 children were randomized to receive study vaccine. MenACWY-CRM met statistical superiority criteria vs. MCV4 for groups W and Y and was noninferior for group C in both age strata. For group A, noninferiority criteria were not met; the group A seroresponse rates for MenACWY-CRM and MCV4, respectively were 72% (95% confidence interval 68–75%) and 77% (73–80%) in 2–5-year-olds and 77% (73–80%) and 83% (79–86%) in 6–10-year-olds. When the two age strata were combined (2–10-year-old children), MenACWY-CRM was noninferior to MCV4 for all four groups, and statistically superior for groups C, W, and Y. Safety parameters were similar across age cohorts and vaccine groups.

Conclusions: MenACWY-CRM and MCV4 were immunogenic and well tolerated in children aged 2–10 years. Seroresponse to MenACWY-CRM was statistically noninferior to MCV4 for all groups, and statistically superior for groups C, W, and Y.

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1. Introduction

Neisseria meningitidis is a gram-negative diplococcus that causes severe invasive disease including septicemia and meningitis [1]. Most invasive disease is the result of infection with one of five groups (A, B, C, Y, W-135) as characterized by their capsular polysaccharide [2]. Epidemic group A disease occurs in sub-Saharan Africa, the Middle East and in some areas of Asia [3–5]. Endemic group B and C disease predominates in Europe and North America; an increase in group Y disease has been reported over the last 20 years in the United States [6]. Outbreaks of W-135 disease have been reported in the Middle East and Africa [4,7]. Meningococcal disease is seen in all age groups including children 2–10 years of age; in the US, groups A, C, Y and W-135 account for approximately 60% of meningococcal disease [8].

Using similar conjugation technology that led to the development of effective vaccines against Haemophilus influenzae type b and pneumococcal diseases in infants and young children [9,10], group C meningococcal conjugate vaccines (MenC) were devel-
operated that led to dramatic decreases in invasive disease caused by *N. meningitidis* group C in European countries and Australia where universal immunization programs were implemented [11–14]. By chemically conjugating capsular polysaccharide to a protein carrier, the polysaccharide antigen is converted from a T-cell independent antigen to a T-cell dependent antigen with the resultant induction in immune memory in all ages after immunization and improved immunogenicity in infants [15–17].

A quadrivalent meningococcal conjugate vaccine was developed in an attempt to improve upon the quadrivalent meningococcal polysaccharide vaccine that has been available for decades. Menactra® (MCV4; Sanofi Pasteur, Swiftwater, PA) was licensed for use in the United States January 17, 2005, for individuals 11–55 years of age and October 19, 2007, for children 2–10 years of age, and is recommended for universal use as a preadolescent dose [18] and for children 2–10 years of age with increased risk of meningococcal infection [19,20]. Menveo® (MenACWY-CRM; Novartis Vaccines and Diagnostics, Cambridge, MA), a quadrivalent meningococcal conjugate vaccine, was recently licensed in the United States February 19, 2010, for individuals 11–55 years of age and in Canada on May 21, 2010 for individuals 11 years and older; further studies were undertaken to support its use in infants [21–23] and younger children [24]. The purpose of this study was to compare the safety and immunogenicity of MenACWY-CRM to the licensed MCV4 vaccine in children 2–10 years of age.

### 2. Methods

#### 2.1. Vaccines

The investigational quadrivalent meningococcal conjugate vaccine (MenACWY-CRM; Menveo®, Novartis Vaccines and Diagnostics, Cambridge, MA) contained (per 0.5 mL dose) 10 μg of meningococcal group A capsular polysaccharide and 5 μg each of group C, W-135 and Y capsular polysaccharides conjugated to CRM197 (Table 1). The vaccine was prepared by mixing, just before injection, the MenCWY liquid suspension and the lyophilized MenA powder. The comparison vaccine was the licensed quadrivalent meningococcal vaccine conjugated to diphtheria toxoid (MCV4, Menactra®, Sanofi Pasteur, Swiftwater, PA) containing (per 0.5 mL dose) 4 μg each of meningococcal groups A, C, Y and W135 capsular polysaccharides conjugated to diphtheria toxoid. MCV4 was supplied in single-dose vials and did not require mixing.

#### 2.2. Study population

Healthy children 2–10 years of age who were up to date with their routine childhood immunizations, had never previously received any meningococcal vaccine and had no history of meningococcal infection were recruited into the study at 27 American and 16 Canadian sites. Children were excluded from participation if they had known or suspected HIV infection, were immunocompromised or receiving immunosuppressive therapy, had received immunoglobulin, blood or blood products or any experimental vaccines within 90 days, had a history of neurological disease, developmental delay, seizures, bleeding diathesis, had any serious acute or chronic medical condition, or had a hypersensitivity to any component of the vaccine.

#### 2.3. Study design and procedures

The study was a phase 3, multicenter, partially observer-blind (described below), randomized, controlled trial. Written informed consent was obtained from the parents or guardian prior to any study procedure; the study protocol was approved by the Research Ethics Board or Institutional Review Board of each participating center. Study visits took place from 13 March, 2008 to 14 October, 2009. Participants 2–5 years of age were randomly allocated in a 1:2:2 ratio to receive either two doses of MenACWY-CRM, one dose of MenACWY-CRM or one dose of MCV4. Participants 6–10 years of age were randomly allocated in a 1:1 ratio to receive a single dose of MenACWY-CRM or MCV4. Randomization was achieved within each age stratum using a center-stratified, computer-generated list provided by the Biostatistics and Clinical Data Management Group of Novartis Vaccines and Diagnostics. Participants (2–5 years of age) allocated to the two-dose MenACWY-CRM group received the vaccines in an open-label fashion. Participants either 2–5 or 6–10 years of age allocated to receive a single dose of MenACWY-CRM or MCV4 received their vaccine in an observer-blinded manner.

MenACWY-CRM or MCV4 was given by 0.5 mL intramuscular injection in the left deltoid area. Participants allocated to the two-dose MenACWY-CRM received the second dose after a 60-day interval. All participants were monitored by study staff for 30 min after each injection for immediate reactions. Parents recorded in a standardized symptom diary daily the following solicited symptoms for 7 days after each vaccination: temperatures (axillary route in 2–5-year-olds; oral route in 6–10–year-olds), injection-site reactions (pain, erythema, induration) and systemic reactions (change in eating habits, sleepiness, irritability, diarrhea, arthralgia, headache, rash and fever in 2–5–year-olds and chills, nausea, malaise, myalgia, arthralgia, headache, rash and fever in 6–10-year-olds). Solicited adverse events were either measured (fever, erythema, swelling) or categorized by the parents as mild (no limitation of normal daily activities), moderate (some limitation of normal daily activities) or severe (unable to perform normal daily activities). Medically significant events, such as hospitalizations, and other serious adverse events were collected for six months following vaccination. All unsolicited adverse events were collected and tabulated by preferred term and body system.

Blood was collected by venipuncture immediately before and approximately 28 days after vaccination (after the second dose in the two-dose group). Functional antibody to each of the four meningococcal groups was measured by a serum bactericidal assay using human complement (hSBA) and reported as reciprocal dilution (RD) [21,25,26]. All antibody measurements were performed by Novartis Vaccines and Diagnostics (Marburg, Germany).

#### 2.4. Data analysis and statistical considerations

The primary objective of the study was to compare the immunogenicity of a single dose of MenACWY-CRM with a single dose of MCV4 in children 2–5 years of age and children 6–10 years of age. Immunogenicity was characterized as the percentage of subjects achieving a seroresponse against each of the four groups (A, C, W and Y). Seroresponse was defined as a fourfold or greater rise.

### Table 1

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Quantity per 0.5 mL dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCV4</td>
</tr>
<tr>
<td>Group A polysaccharide</td>
<td>4 μg</td>
</tr>
<tr>
<td>Group C polysaccharide</td>
<td>4 μg</td>
</tr>
<tr>
<td>Group Y polysaccharide</td>
<td>4 μg</td>
</tr>
<tr>
<td>Group W135 polysaccharide</td>
<td>4 μg</td>
</tr>
<tr>
<td>Protein carrier</td>
<td>48 μg&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>4.4 mg</td>
</tr>
<tr>
<td>Sodium phosphate</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Postassium dihydrogen phosphate</td>
<td>–</td>
</tr>
<tr>
<td>Sucrose</td>
<td>–</td>
</tr>
</tbody>
</table>

Each polysaccharide in each vaccine was conjugated to a protein carrier.

<sup>a</sup> Diphtheria toxoid total protein.

<sup>b</sup> CRM<sub>197</sub> toxoid total protein.
in group-specific antibody; in participants with a prevaccination antibody titer <4, seroresponse was defined as an hSBA of ≥8. Secondary objectives included evaluation of the geometric mean hSBA antibody titers (hSBA GMTs) and the proportion of participants achieving hSBA titers ≥8 (seroprotection). Additional secondary objectives were to assess the safety and tolerability of all the vaccines administered and to assess the immunogenicity (as defined by all of the above immunogenicity parameters) of two doses of MenACWY-CRM in children 2–5 years of age.

All subjects who received at least one dose of vaccine were included in the safety analysis. Adverse events were tabulated and the maximum severity reported for each time period was used. The proportion of participants having an adverse event by vaccine group was calculated with 95% confidence intervals (CIs).

All subjects who received all the protocol-specified doses of vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to database lock and unblinding were part of the per-protocol immunogenicity analysis population. A major protocol violation was defined as one that was considered to have a significant impact on the immunogenicity results of the subject. The percentage of participants with a seroresponse or who were seroprotected, along with the associated Clopper–Pearson 95% confidence intervals, were computed. Immunogenicity of MenACWY-CRM was considered noninferior to MCV4 for any of the 4 groups if the lower limit of the two-sided 95% confidence interval around the difference of the percentage of participants with a seroresponse (or hSBA ≥8) for that group (MenACWY-CRM minus MCV4) was greater than −10%. A MenACWY-CRM group was considered to have a statistically superior immune response compared to MCV4 if the lower limit of the two-sided 95% confidence interval around the difference in percentage of participants was greater than 0 (i.e., the CI did not include 0). Geometric mean titers (GMTs) and two-sided 95% CIs were calculated for each vaccine group and for each group pre- and postvaccination by exponentiating (base 10) the least-squares means of the logarithmically transformed (base 10) titers and their 95% CIs obtained from a two-way Analysis of Variance (ANOVA) with factors for vaccine group and center. Titers below the detection limit were set to half that limit for the purpose of analysis. As an additional secondary objective analysis, the immunogenicity of the combined group of children aged 2–10 years was analyzed.

A sample size of 680 per group in the 2–5-year-olds and 560 per group for the 6–10-year-olds was estimated to provide 95–99% power to demonstrate noninferiority for each of the four groups, 88% power within each age group to demonstrate noninferiority for all four groups and 77% power to show noninferiority of all four groups across both age strata (2–10 years of age). Inclusion of 325 participants who received the two-dose MenACWY-CRM regimen was calculated to provide 84–94% power to demonstrate superiority of the two-dose regimen in children 2–5 years of age at alpha of 0.05.

3. Results

3.1. Demographics and participant disposition

A total of 2907 children between 2 and 10 years of age were enrolled in the study. There were 1751 children 2–5 years of age randomly allocated 1:2:2 to receive two doses of MenACWY-CRM (n = 359), one dose of MCV4 (n = 696), or one dose of MenACWY-CRM (n = 696). There were 1156 children 6–10 years of age randomly allocated 1:1 to receive MCV4 (n = 574) or MenACWY-CRM (n = 582). The male/female distribution, race, and weight and height were similar within each age stratum (Table 2).

In total, 2802 (96.4%) participants completed the protocol (Fig. 1). There were 105 premature withdrawals (26 in the two-dose MenACWY-CRM group, 27 in the single-dose MenACWY-CRM 2–5-year-old group, 24 in the single-dose MCV4 2–5-year-old group, 11 in the single-dose MenACWY-CRM 6–10-year-old group and 17 in the single-dose MCV4 6–10-year-old group). For the entire participant population, 68 participants withdrew as a result of loss to follow-up, 28 participants withdrew consent, 4 subjects were deemed to be ineligible according to the inclusion and exclusion criteria, three participants were withdrawn because of a protocol violation, one for an administrative reason, and one withdrew after consent was obtained but prior to vaccination. There were no withdrawals related to an adverse event. An additional 9 enrolled subjects did not receive a vaccine due to withdrawal of consent (n = 7), inappropriate enrollment (n = 1) or inability to obtain baseline serology (n = 1); all subjects who received a dose of the vaccine were included in the safety analysis to the extent that data were available. A total of 279 participants (including the 9 participants who were unvaccinated) were excluded from the per-protocol immunogenicity analysis. The main reason for exclusion was a missing prevaccination (n = 60) or postvaccination (n = 130) specimen. Ten subjects who received the wrong vaccine product were excluded from the immunogenicity analysis but included “as treated” in the safety analysis.

3.2. Adverse events

Local or systemic adverse events after vaccination with a single dose of MenACWY-CRM or MCV4 were common, reported by 60% and 51%, respectively (Tables 3a and 3b). Erythema and pain were the most commonly reported injection-site reactions in both the 2–5 and 6–10 years age groups; in the 2–5 years age...
group, there were no differences between the vaccines. In the 6–10 years age group, significantly fewer participants reported pain after MenACWY-CRM than MCV4 (39% vs. 45%; \(p = 0.039\)). In contrast, fewer MCV4 than MenACWY-CRM recipients reported injection-site erythema (22% vs. 28%; \(p = 0.017\)). Severe pain or erythema >100 mm in the 6–10 years age group was unusual postvaccination with non significant trends toward higher rates of erythema post-MenACWY-CRM and pain post-MCV4.

Rates of systemic adverse events were similar in recipients of MenACWY-CRM and MCV4 (Tables 3a and 3b). In the 2–5-year-old children, irritability was the most common reported systemic adverse event (21% and 22%, respectively), followed by sleepiness (16% and 18%, respectively); fever \(\geq 38^\circ\)C was only reported by 2% of participants. Headache was the most common systemic adverse event in the 6–10-year-old children, reported by 18% of MenACWY-CRM recipients and 13% of MCV4 recipients (\(p = 0.049\)). There were no differences between the groups for any other systemic adverse events. Most adverse events in the 2–5 and 6–10 years age groups were reported as mild; rates of severe adverse events never exceeded 2% for either vaccine.

There were also no differences between the groups in the rates of non solicited adverse events between the MenACWY-CRM (26%) and the MCV4 (24%) groups (data not shown). Most of these adverse events (10% and 11%, respectively) were related to minor intercurrent infectious diseases such as upper respiratory tract infection.

An adverse event was reported by 72% of two-dose recipients, likely reflecting receipt of an additional dose and thus two seven-day observation periods. In the two-dose group, adverse events

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### Table 3a

Percent (95% confidence interval) of 2–5-year-olds with solicited reactions by vaccine group.

<table>
<thead>
<tr>
<th>Injection-site reactions</th>
<th>Single dose</th>
<th>Two doses MenACWY-CRM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCV4 (n=684) % (95% CI)</td>
<td>MenACWY-CRM (n=693) % (95% CI)</td>
</tr>
<tr>
<td>Erythema</td>
<td>25 (22–28)</td>
<td>27 (24–30)</td>
</tr>
<tr>
<td>Induration</td>
<td>18 (16–22)</td>
<td>18 (15–21)</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in eating</td>
<td>10 (8–13)</td>
<td>9 (7–12)</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>18 (16–22)</td>
<td>16 (13–19)</td>
</tr>
<tr>
<td>Irritability</td>
<td>22 (19–26)</td>
<td>21 (18–24)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (6–10)</td>
<td>7 (5–9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (2–5)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (4–8)</td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (3–7)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Fever (\geq 38^\circ) C</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
</tr>
</tbody>
</table>

No statistically significant differences were observed for the primary comparison between the single-dose groups. Percentages are based on numbers of children for whom diary card data were available.
were reported less frequently after the second dose (47%) compared to the first dose (63%). Rates of injection-site reactions after the second dose (28%) in the two-dose MenACWY-CRM group were similar to the rates after the first dose (32%) in the two-dose MenACWY-CRM group and the single-dose MenACWY-CRM group (33%). There were no differences in severe injection-site reactions after the first or second dose. Irritability was also the most common systemic adverse event after the second dose of MenACWY-CRM. There were no differences in rates of any systemic adverse events after the first or second dose.

Serious adverse events were reported by a total of 17 participants during the trial and were all related to hospitalization; none were assessed as vaccine-related by the investigators. There were two participants that reported a serious adverse event in the MenACWY-CRM two-dose group (a parvovirus infection and intestinal obstruction in one participant and pneumonia in a second participant), eight participants with serious adverse events in the MenACWY-CRM one-dose group (one multiple traumatic injuries, two pneumonias, one bronchial hyper-reactivity, one dehydration, one peritonsillar abscess and a shigella and staphylococcal infection). Most of these events occurred more than 6 weeks after vaccination.

### 3.3. Immunogenicity

In the 2–5-year-old children, seroresponse was higher for recipients of MenACWY-CRM than MCV4 for group W-135 (72% vs. 58%) and group Y (56% vs. 45%) and similar for group C (60% vs. 56%); non-inferiority criteria were met for these three groups and statistical superiority of MenACWY-CRM was demonstrated for groups W-135 and Y (Table 4). Group A response after MenACWY-CRM (72%) did not achieve the noninferiority criterion compared to MCV4 (77%). In 6–10-year-old children, noninferiority criteria and statistical superiority of MenACWY-CRM compared to MCV4 was also demonstrated for group W-135 (57% vs. 44%) and group Y (58% vs. 39%); noninferiority criteria were met for group C (63% vs. 57%) but not for group A (77% vs. 83%). For the combined 2–10 year age cohort, noninferiority criteria were demonstrated for all four groups and statistical superiority was demonstrated for groups C, W-135 and Y.

Prevaccination hSBA levels against all 4 groups were similar amongst the vaccine groups (Table 5). A significant rise in hSBA titers was demonstrated against all four groups in children 2–5 and 6–10 years of age. Significantly higher postvaccination hSBA titers were found against group C, W-135 and Y in recipients of MenACWY-CRM than MCV4; hSBA titers against group A were similar after either vaccine. Seroprotection rates, as defined as hSBA titers ≥8, were similar prevaccination. Postvaccination, seroprotection rates were higher for groups W-135 and Y, lower for group A and similar for group C in both 2–5 and 6–10-year-old children (Fig. 2).

Baseline hSBA GMTs (Table 5) and seroprotection levels were similar for all groups before vaccination in the single- or two-dose MenACWY-CRM, 2–5-year-old groups. Postvaccination, seroresponse, seroprotection and hSBA GMT were all significantly higher (p < 0.001) in recipients of two doses of MenACWY-CRM than in recipients of a single dose (Tables 4 and 5 and Fig. 2).

### 4. Discussion

The purpose of this study was to assess the safety and immunogenicity of a quadrivalent vaccine, MenACWY-CRM, currently licensed for use from 11 to 55 years of age, in children 2–10 years of age in comparison with a quadrivalent vaccine (MCV4) already licensed in this younger age group. The results of the study demonstrate that MenACWY-CRM was well tolerated and immunogenic in these young children and with a similar safety profile and favorable immunogenicity profile compared to the licensed MCV4 product. The data from this study, along with the data that supported the licensure of the vaccine in adolescents and adults, previously published data using two or three doses in the first year of life [21,22] and a single-dose schedule at 12 or 18 months of age [23], now demonstrate the safety and immunogenicity of MenACWY-CRM across the age spectrum from infancy to 55 years of age.

As a result of the relatively low incidence of meningococcal disease, studies demonstrating the efficacy of new meningococcal vaccines are impractical. Instead, licensure of new products is based on demonstrating noninferiority in the immune response to the

### Table 3b

Percent (95% confidence interval) of 6–10-year-olds with solicited reactions by vaccine group.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>MCV4 (n = 571)</th>
<th>MenACWY-CRM (n = 582)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>22 (19–26)</td>
<td>28 (25–32)</td>
</tr>
<tr>
<td>Induration</td>
<td>13 (10–16)</td>
<td>17 (14–20)</td>
</tr>
<tr>
<td>Pain</td>
<td>45 (41–49)</td>
<td>39 (35–43)</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>5 (3–7)</td>
<td>5 (4–7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (5–9)</td>
<td>8 (6–11)</td>
</tr>
<tr>
<td>Malaise</td>
<td>11 (8–14)</td>
<td>14 (11–17)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (8–13)</td>
<td>10 (8–13)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (3–6)</td>
<td>6 (5–9)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (11–17)</td>
<td>18 (15–21)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (2–5)</td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>Fever ≥38°C</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
</tr>
</tbody>
</table>

Percentages are based on numbers of children for whom diary card data were available.

*p < 0.05 vs. comparator; no other statistically significant differences were observed.

### Table 4

Seroresponse after one dose of MCV4 or MenACWY-CRM or two doses of MenACWY-CRM in children 2–10 years of age (per protocol population).

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion (95% confidence interval) with seroresponse*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2–5 years</td>
</tr>
<tr>
<td></td>
<td>MCV4 1-dose</td>
</tr>
<tr>
<td></td>
<td>(n = 600–615)</td>
</tr>
<tr>
<td>A</td>
<td>77 (73–80)</td>
</tr>
<tr>
<td>C</td>
<td>56 (52–60)</td>
</tr>
<tr>
<td>Y</td>
<td>45 (41–49)</td>
</tr>
<tr>
<td>W-135</td>
<td>58 (54–62)</td>
</tr>
</tbody>
</table>

* Seroresponse was defined as a ≥4-fold rise in group-specific hSBA antibody; in participants with a prevaccination antibody titer <4, seroresponse was defined as an hSBA titer ≥8.
vaccine using immunological surrogates of protection [27]. Based on the landmark studies of Goldschneider and colleagues in the 1960s [26], bactericidal activity at a serum dilution of 1:4 using human complement was correlated with protection against invasive meningococcal disease. More recently, Trotter and colleagues confirmed the inverse correlation of serum bactericidal titer (using rabbit serum and a threshold of 1:8) and incidence of invasive serogroup C meningococcal disease in the United Kingdom prior to universal immunization [28]. However, given the variability observed with biological assays, many regulatory authorities prefer the use of a 1:8 threshold as a surrogate measurement of protection [29]. In contrast to seroprotection where one posits that the presence of a certain level of antibody will correlate with protection against invasive disease, comparative vaccine studies benefit from a more nuanced analysis. Seroresponse is a measure of an individual’s immune response to a meningococcal antigen that may provide a more complete comparative picture of vaccine response, including those populations with elevated baseline antibody titers. In this study, seroresponse was defined as the development of seroprotective antibody levels in individuals previously seronegative to the specific capsular antigen or a four fold or greater increase in antibody in individuals already seropositive to that antigen. Although these measures of immune response and correlates of protection are based on empiric data and are widely accepted, one must use caution in interpreting them on an individual level. Cases of invasive disease have occurred in individuals with antibody levels in excess of the “protective level” and protection provided by the vaccine under conditions of programmatic use (field effectiveness) have exceeded what would have been predicted using these thresholds [26,30,31].

![Figure 2](http://example.com/fig2.png)

**Figure 2.** Proportion of participants achieving hSBA titer ≥8 postvaccination in children 2–5 years of age after receiving one or two doses of MenACWY-CRM or one dose of MCV4 (panel A), 6–10 years of age receiving one dose of MenACWY-CRM or MCV4 (panel B), and children 2–10 years of age following a single dose of MCV4 or MenACWY-CRM (panel C). White bars represent MCV4, black bars represent MenACWY-CRM, and striped bars two doses of MenACWY-CRM. Error bars represent the 95% confidence interval.
The importance of achieving titers beyond the accepted sero-protection level has not been clearly defined. The geometric mean antibody titer reflects at a population level the magnitude of the vaccine response and may be predictive of the duration of protection in diseases where protection is dependent on the presence of pre-existing antibody. In addition to the statistically superior seroresponse rates against group Y and W-135 after MenACWY-CRM, significantly higher geometric mean antibody titers were achieved against groups C, Y, and W-135. Superior seroresponses against groups A, W-135, and Y for MenACWY-CRM when compared with MCV4 have also been observed in another study of these vaccines in adolescents [32]. Long-term follow-up of participants for immunogenicity testing is planned but whether higher hSBA GMTs at one month postvaccination would lead to a longer duration of protection can only be determined through disease surveillance after widespread use of such vaccines.

The results of this study demonstrated that a single-dose regimen of the MenACWY-CRM vaccine compared favorably to the licensed MCV4 vaccine in children 2–10 years of age. Although similar (and for some groups superior) to the licensed MCV4, immune responses (as measured by seroresponse, seroprotection or geometric mean antibody titer) to MenACWY-CRM appeared to increase with age. Although seroresponse and seroprotection rates in the 2–5-year-olds and 6–10-year-olds were similar, geometric mean antibody titers tended to be higher in the older age group. Dramatic increases in rates of seroresponse, seroprotection, and geometric mean antibody titers were achieved with a second dose of MenACWY-CRM two months later without any increase in reported adverse events. These data demonstrate that, as with infants and toddlers [21–23], MenACWY-CRM can be safely and effectively given in a two-dose schedule should higher rates of seroresponse or seroprotection be desirable or if higher antibody levels are demonstrated to increase the duration of protection. Mathematical modeling, cost–benefit analyses, and longer-term follow-up of vaccine recipients might inform these decisions.

Given the variable epidemiology and geographic distribution of different groups of meningococcal disease [3–6], one can anticipate that meningococcal immunization policy will vary regionally in both the age of immunization and the product used (meningococcal C conjugate vaccine or quadrivalent meningococcal conjugate vaccine). In the United Kingdom, where group C disease predominated, universal monovalent meningococcal C conjugate vaccine programs were implemented and dramatically reduced the incidence of invasive disease [13,17]. In the United States, where invasive disease caused by group Y has emerged over the past decade, universal preadolescent immunization programs were implemented with the quadrivalent meningococcal conjugate vaccine [2,18–20]. In other countries, such as Canada, universal infant or toddler immunization programs were implemented in all provinces with meningococcal C conjugate vaccine, with some provinces choosing to provide broader meningococcal protection by immunizing all preadolescents with the quadrivalent meningococcal conjugate vaccine [33]. Finally, due to the unique epidemiology of meningococcal disease where, in contrast to Haemophilus influenzae type b and pneumococcal disease, a second peak of incidence occurs later, the need for and timing of a booster vaccination is a topic of active debate [34]. Given the constantly changing epidemiology of invasive meningococcal disease, the availability of a quadrivalent meningococcal vaccine that is immunogenic and well-tolerated in all ages will provide more programmatic flexibility by providing broader coverage to all age groups with a single product.

In summary, this study demonstrated that MenACWY-CRM (Menveo®, Novartis Vaccines and Diagnostics), which is currently licensed in the United States, Canada, Australia and Europe for individuals 11–55 years of age, is immunogenic and well-tolerated in children 2–10 years of age and compares favorably to MCV4 (Menactra®, Sanofi Pasteur) that was previously licensed for this age group. With previous studies demonstrating the safety and immunogenicity of MenACWY-CRM in infants and toddlers, a single product may soon be available to provide broad protection against groups A, C, Y and W-135 across the age spectrum from infancy to 55 years of age.

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