Safety and Immunogenicity of a Meningococcal Quadrivalent Conjugate Vaccine in Five-to Eight-Year-Old Saudi Arabian Children Previously Vaccinated with Two Doses of a Meningococcal Quadrivalent Poly saccharide Vaccine

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Saudi Arabian children respond poorly to 2 doses of meningococcal quadrivalent polysaccharide vaccine (MPSV4) when given before 2 years of age. This study examined whether such children were able to respond to 1 dose of quadrivalent meningococcal diphtheria toxoid conjugate vaccine (MCV4) when they were older. Saudi Arabian children 5 to 8 years of age who had previously been vaccinated with 2 doses of MPSV4 when they were under 2 years of age (termed the prior-MPSV4 group) were enrolled in a controlled, open-label, multicenter study. In the prior-MPSV4 group, children (n = 153) received 1 dose of MCV4, as did a group of age-matched meningococcal vaccine-naïve children (n = 85). Blood samples collected prevaccination and 28 days postvaccination were measured for serogroup-specific serum bactericidal antibody (SBA) levels in the presence of baby rabbit complement (rSBA) and for IgG antibody levels. Vaccine tolerability and safety were also evaluated. For all of the measured serogroups (A, C, Y, and W-135), the meningococcal vaccine-naïve participants achieved higher postvaccination rSBA geometric mean titers (GMTs) than did those in the prior-MPSV4 group. This was statistically significant for serogroup C (512 versus 167). Percentages of participants with postvaccination titers of ≥8 and with ≥4-fold increases in prevaccination to postvaccination titers appeared to be quite similar in the 2 groups. No worrisome safety signals were detected. MCV4 induced robust immune responses and was well tolerated in Saudi Arabian children who previously received 2 doses of MPSV4 as well as in those who were previously meningococcal vaccine naïve.

Meningococcal disease epidemic characteristics vary depending on location, serogroup, age group, and season of the year. During the last 50 years, epidemics of serogroup A disease have typically occurred in sub-Saharan Africa (the Meningitis Belt), while serogroup B and C disease has been endemic in other regions of the world. Epidemics of meningococcal disease in the Kingdom of Saudi Arabia (KSA) are associated with a unique feature: a yearly influx of visitors from around the world who perform Hajj and Umra. Approximately 2.4 million pilgrims attended the 2008 Hajj season, of which 71.8% came from outside the KSA (19). Many of these pilgrims originate from areas where invasive meningococcal disease is endemic, such as from the Meningitis Belt, thus increasing the risk of meningococcal disease outbreaks in the KSA during these periods of massive gatherings.

The Hajj pilgrimage to Mecca has historically been associated with outbreaks of meningococcal serogroup A disease. The main means of prevention against meningococcal disease was the bivalent serogroup A and C polysaccharide vaccine (1, 4). During the Hajj pilgrimages of 2000 and 2001, there was an epidemiologic shift from serogroup A disease to serogroup W-135 disease, together with an increased incidence in younger age groups (9, 15, 18). This prompted the KSA Ministry of Health (MoH) to introduce vaccination with meningococcal quadrivalent polysaccharide (serogroups A, C, Y, and W-135) vaccines (MPSV4). MPSV4 was recommended for those coming for Hajj and for school children in the KSA. However, it was observed that 58% of reported meningococcal disease occurred below the age of 5 years, with 39% of cases occurring below 2 years of age (3). Thus, for forthcoming Hajj seasons the KSA MoH launched a vaccination campaign with MPSV4, targeting children from 6 months to 5 years of age. The campaign was conducted in 2003 and included an immunogenicity study to evaluate the immune response to serogroups A, C, Y, and W-135 (2, 11). These studies clearly demonstrated the poor immunogenicity of the serogroup C, Y, and W-135 polysaccharides in children between 3 months and 2 years of age; hence, the KSA MoH changed its recommendation to specify that only those ≥2 years of age should receive MPSV4. These interventions have largely controlled meningococcal disease since 2002 (12).

A quadrivalent (A, C, Y, and W-135) meningococcal diphtheria toxoid-conjugate vaccine (MCV4; Menactra; Sanofi Pasteur Inc., Swiftwater, PA) has been licensed since 2005 in the United States for administration to 11 to 55 year olds and in 2007 for 2 to 10 year olds by the U.S. Food and Drug Administration (FDA) (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109013.htm). In March 2011, licensure was approved in KSA for those 2 to 55 years of age (http://www.sanofipasteur.com/articles/75-sanofi-pasteur...
MATERIALS AND METHODS

A phase 3, open-label, controlled trial was conducted at 4 sites in the KSA. The final study protocol was approved by the Medical Research Ethics Committee of the MoH of KSA (an independent ethics committee) before study initiation. Written informed consent was obtained from the participant’s parent or legal representative. Good clinical practice and all applicable local regulations were observed throughout the study.

Participants. Healthy children 5 to 8 years of age were recruited into 2 groups. For inclusion in the prior-MPSV4 group, children must have received 2 doses of MPSV4 before 2 years of age. For inclusion in the meningococcal vaccine-naive group, participants must have had no history of meningococcal vaccination. Children were excluded from the study if they had a serious, unstable chronic disease; known or suspected immunologic impairment; acute illness; received systemic antibiotics 6 weeks before study entry; an oral temperature of ≥37.5°C at study entry; received immunoglobulins or other blood products <3 months before study entry or systemic corticosteroids <6 weeks before study entry; received or were scheduled to receive any vaccine <14 days before or <14 days after study entry; a history of meningococcal disease; hypersensitivity to any vaccine component; participated in a study <4 weeks previous or concurrent with the present study; or a personal or family history of Guillain–Barre syndrome.

Interventions. All participants (prior-MPSV4 and meningococcal vaccine-naive groups) received a single, 0.5-ml, intramuscular injection of MCV4 in the deltoid region. Immediately before vaccination and at a visit 28 days postvaccination (±7 days), approximately 5 ml of blood was collected by standard venipuncture.

Serology. Participant sera were analyzed for each meningococcal serogroup (A, C, Y, and W-135) by the serum bactericidal antibody (SBA) assay as previously described (17); the complement source was baby rabbit sera (rSBA; Pel-Freeze Incorporated, Rogers, AR). The SBA target strains were F8238 (A:4,21P1.21), C11 (C:16,P1.7-1,1), M03.0 241125 (Y:2a,P1.5,2), and M01 240070 (W135:NT:P1.18-1,3). SBA titers were expressed as the reciprocal of the final serum dilution resulting in 50% killing after 60 min of incubation. For computational purposes, SBA titers from baseline to 28 days postvaccination were determined. For serogroup–specific IgG evaluations, geometric mean concentrations (GMC) together with 95% CIs were calculated. P value comparisons between the GMCs in each study group were performed by t test. The t test was performed on the log10 transformation of the titers, and consequently a normal distribution was assumed. The equality of the variance was checked with the distribution of the log10 titers. P value comparisons between the proportions of participants with ≥4-fold increases in rSBA titers from baseline to 28 days postvaccination were performed with the chi-squared test or Fischer’s exact test.

Safety outcomes by study group were assessed on the basis of reports of immediate reactions ≤30 min postvaccination, solicited injection-site reactions (pain, erythema, and swelling), and systemic reactions (fever, headache, malaise, and myalgia) ≤7 days postvaccination, unsolicited adverse events (AEs) from vaccination until a scheduled visit at 28 days postvaccination, and serious AEs through 28 days postvaccination. The immunogenicity set was defined as participants who satisfied inclusion and exclusion criteria, received a study-related dose of MCV4, provided a serum sample 21 to 35 days postvaccination, and received no prohibited concomitant therapy during the study. The safety set was defined as all participants who received a dose of MCV4 and who had safety data available. Parents of participants were given diary cards and asked to record the occurrence and intensity (grade 1, 2, or 3 in order of increasing intensity) of injection-site reactions and systemic reactions. The 95% CIs for the rates of solicited adverse reactions were calculated by the exact binomial distribution for percentages (Clopper-Pearson) for each reaction and each study group. The nature of unsolicited AEs was described by the Medical Dictionary for Regulatory Activities, Preferred Terms (MedDRA-PT); AE time of onset, duration, and whether a causal relationship to vaccination existed was also noted. Unsolicited AEs were also reported on diary cards.

RESULTS

Participant flow and demographics. The study was conducted between 30 September 2007 and 2 December 2007 (at recruitment and 28-day follow-up visits), and 238 participants received 1 dose of MCV4 (153 in the prior-MPSV4 group and 85 in the meningococcal vaccine-naive group). The flow of participants through the

| Group                  | No. of planned participants | No. who received MCV4 | No. in safety analysis set | No. who completed study | No. who withdrew voluntarily | No. showing immunogenicity |
|------------------------|-----------------------------|-----------------------|----------------------------|-------------------------|-------------------------------|----------------------------|
| Prior-MPSV4            | 150                         | 153                   | 151                        | 151                     | 2                             | 140                        |
| Meningococcal vaccine naïve | 75                          | 85                    | 85                         | 84                      | 1                             | 81                         |
| Total                  | 225                         | 238                   | 236                        | 235                     | 3                             | 221                        |

a Two participants were excluded because their diary cards were not available.
b Participants later determined not to meet inclusion criteria included 9 in the prior-MPSV4 group (did not receive 2 doses before age 2 years) and 2 in the meningococcal vaccine-naïve group (were not between 5 and 8 years old). Two participants in each group had no blood sample at postvaccination visit, and one participant in the prior-MPSV4 group had a blood sample at a postvaccination visit outside the time window. One participant in the prior-MPSV4 group had prohibited concomitant therapy during the study.
study and the rationale for excluding some participant data from subsequent analysis are presented in Table 1.

Among the study participants who received 1 dose of MCV4, 55.0% were girls (54.9% in the prior-MPSV4 group and 55.3% in the meningococcal vaccine-naive group); the mean age at the time of vaccination was 6.3 years (prior-MPSV4 group, 6.1 years; meningococcal vaccine-naive group, 6.5 years). Among participants, the ages ranged between 4.8 and 8.9 years of age. Participants in the prior-MPSV4 group received their second dose of MPSV4 vaccine 4 to 7 years previously; the mean elapsed time in the meningococcal vaccine-naive group, 6.5 years). Among participants, the mean age at the time of vaccination was 6.3 years (prior-MPSV4 group, 6.1 years; meningococcal vaccine-naive group, 6.5 years). Among participants, the ages ranged between 4.8 and 8.9 years of age. Participants in the prior-MPSV4 group received their second dose of MPSV4 vaccine 4 to 7 years previously; the mean elapsed time was 3.8 months (median, 57 months; range, 48 to 82 months).

Immunogenicity. As shown in Table 2, there were no significant differences in either the pre- or postvaccination rSBA GMTs for serogroups A, Y, and W-135 between the meningococcal vaccine-naive group and the prior-MPSV4 group. For serogroup C, the rSBA GMTs in the meningococcal vaccine-naive group were statistically higher both prevaccination (4.1 versus 2.5; \( P = 0.001 \)) and postvaccination (512 versus 167; \( P < 0.001 \)). The proportion of participants who achieved serogroup C postvaccination rSBA titers of \( \geq 8 \) was also greater in the meningococcal vaccine-naive group (95.1% versus 86.4%; \( P = 0.065 \) by Fisher’s exact test). For serogroups A, Y, and W-135, all children achieved postvaccination titers of \( \geq 8 \). There were no significant differences between groups as assessed by a \( \geq 4 \)-fold increase in rSBA titer from baseline. Reverse cumulative distribution curves for SBA titers for each serogroup are shown in Fig. 1.

Table 3 compares the pre- and postvaccination serogroup-specific IgG GMCs for the meningococcal vaccine-naive and prior-MPSV4 groups. These data show that serogroup A, Y, and W-135-specific IgG GMCs were higher in the prior-MPSV4 group than in the meningococcal vaccine-naive group after MCV4 vaccination; however, the 95% CIs of the study groups overlapped except for serogroup A. The postvaccination serogroup C-specific IgG GMC was approximately equal in both groups, as were the GMCs for all prevaccination sera.

Safety analysis. One immediate unsolicited AE was reported in the prior-MPSV4 group: nasopharyngitis of mild intensity. This AE was deemed unrelated to vaccination. A summary of solicited injection-site and systemic reactions reported during the study is presented in Table 4 (solicited reaction intensity grades are presented in footnote a of Table 4). A substantial majority (\( > 87\% \)) for each category of solicited injection-site reaction types were grade 1; reduced majorities were reported for malaise in the prior-MPSV4 group (61%) and fever in both study groups (50% in the prior-MPSV4 group, 62% in the meningococcal vaccine-naive group). Most reactions resolved in \( \leq 3 \) days. For all types of solicited AEs, the prior-MPSV4 group and the meningococcal vaccine-naive group were similar.

One grade 3 solicited reaction was reported for pain at the injection site on day 2. The AE resolved within 2 days without treatment. Of all solicited systemic reaction reports, 3 participants reported grade 3 fever (1 in the prior-MPSV4 group and 2 in the meningococcal vaccine-naive group). Of these reports, 2 resolved within 3 days after the administration of medication. One participant in the comparison group experienced fever that required contact with a health care professional and the administration of fever-reducing medication; the fever resolved after 10 days.

Four severe unsolicited AEs were reported during the study: 1 headache and 1 upper respiratory tract infection in the prior-MPSV4 group, and 1 case of pharyngitis and 1 upper respiratory tract infection in the meningococcal vaccine-naive group. All reports of unsolicited AEs were considered not to be related to vaccination. One participant experienced 2 separate serious AEs that
were not vaccination related. This participant was admitted to the hospital for an appendectomy and subsequently developed an infection in the incision; the participant recovered completely. There were no deaths and no AEs leading to premature discontinuation during the study.

DISCUSSION

The effect of 2 doses of polysaccharide vaccine on the response to a subsequent dose of conjugate vaccine in young children for serogroups A, C, Y, and W-135 had been unexamined to date. This study demonstrated that MCV4 was safe and induced protective immune responses in children who have previously received 2 doses of MPSV4. After MCV4 vaccination, the rSBA GMT responses appeared to be higher for all serogroups, especially for serogroup C, in those who were meningococcal polysaccharide vaccine naïve compared to those who had received MPSV4. In previous studies, repeated doses of serogroup C polysaccharide vaccine have been clearly documented to lead to immune hyporesponsiveness, while booster antibody responses have been observed for serogroup A with repeat dosing, underscoring the differences in these polysaccharide antigens (8, 10, 14).

The effects of previous serogroup C polysaccharide vaccinations on responses to conjugate vaccination were studied in children in the United Kingdom (6). In this study, 54 children (median age, 34 months; range, 4 to 62 months) previously vaccinated with a single dose of bivalent serogroup A and C meningococcal polysaccharide vaccine (MPV) were revaccinated 7 months later with monovalent serogroup C meningococcal conjugate vaccine (MCV). Their responses were compared to those from 122 MPV-naïve children who received only serogroup C MCV. For children vaccinated with MPV at 1 year of age (median age was estimated to be 8 months with a range of 5 to 11 months), the proportion of children with serogroup C rSBA titers of ≥8 as well as the rSBA GMTs were significantly lower than those for MPV-naïve children. For children vaccinated with MPV between 1 and 5 years of age, rSBA GMTs and the proportion of children protected after MCV administration were similar to those in the MPV-naïve children. Thus, the magnitude of the depressing effect by prior MPV on serogroup C responses to MCV is age dependent, with the greatest effect observed when MPV was administered to infants and young children. The difference between the serogroup C response to conjugate vaccination after prior polysaccharide treatment in the study reported here and the study conducted by Borrow et al. (6) is the time between polysaccharide administration and conjugate vaccination, with a time gap of several years in this study.

TABLE 3 IgG GMCs specific to serogroups A, C, Y, and W-135 at baseline and 28 days postvaccination

| Serogroup and time point | GMC (in µg/ml) (95% CI) by group |
|-------------------------|---------------------------------|
|                         | Prior-MPSV4 | Meningococcal vaccine naïve |
|                         | (n = 140)   | (n = 81)                   |
| Baseline                |             |                              |
| A                       | 1.01 (0.84–1.20) | 1.25 (1.04–1.50)                  |
| C                       | 0.19 (0.15–0.23) | 0.13 (0.09–0.18)                  |
| Y                       | 0.16 (0.14–0.19) | 0.19 (0.15–0.23)                  |
| W135                    | 0.19 (0.16–0.22) | 0.15 (0.12–0.18)                  |
| Postvaccination          |             |                              |
| A                       | 72.11 (57.19–90.92) | 37.17 (27.68–49.91)            |
| C                       | 14.62 (11.59–18.44) | 14.81 (11.38–19.30)            |
| Y                       | 11.00 (8.57–14.11) | 7.89 (5.63–11.05)             |
| W135                    | 7.23 (5.48–9.54) | 5.07 (3.56–7.20)             |
measurements that only assess capsular polysaccharide-specific isotype. This is opposed to serogroup-specific IgG concentration protection, as it detects vaccine-elicited antibodies regardless of Thus, the assay more completely assesses vaccine response and functional antibody against the whole meningococcus strain. quantitation of meningococcal antibody responses (5), measures tween the 2 groups did not differ; this reflects the differences be-

**TABLE 4** Reports of solicited adverse reactions ≤7 days postvaccination by study group^a^

| Site and adverse reaction | Prior-MPSV4 group (n = 151) | Meningococcal vaccine-naive group (n = 85) |
|--------------------------|-----------------------------|------------------------------------------|
|                          | % Grade 1 (n) | % Total (n) | 95% CI          | % Grade 1 (n) | % Total (n) | 95% CI          |
| **Injection site**       |               |             |                 |               |             |                 |
| Pain                     | 19.2 (29)     | 21.2 (32)   | 15.0–28.6       | 16.5 (14)     | 17.6 (15)   | 10.2–27.4       |
| Erythema                 | 6.0 (9)       | 6.6 (10)    | 3.2–11.8        | 9.4 (8)       | 9.4 (8)     | 4.2–17.7        |
| Swelling                 | 6.6 (10)      | 7.3 (11)    | 3.7–12.7        | 8.2 (7)       | 9.4 (8)     | 4.2–17.7        |
| **Systemic**             |               |             |                 |               |             |                 |
| Fever                    | 5.3 (8)       | 10.6 (16)   | 6.2–16.6        | 5.9 (5)       | 9.4 (8)     | 4.2–17.7        |
| Headache                 | 7.3 (11)      | 8.6 (13)    | 4.7–14.3        | 4.7 (4)       | 5.9 (5)     | 1.9–13.2        |
| Malaise                  | 7.3 (11)      | 11.9 (18)   | 7.2–18.2        | 11.8 (10)     | 12.9 (11)   | 6.6–22.0        |
| Myalgia                  | 11.2 (17)     | 13.9 (21)   | 8.8–20.5        | 10.6 (9)      | 11.8 (10)   | 5.8–20.6        |

^a The extent of erythema and swelling at the injection site was measured as grade 1, < 2.5 cm; grade 2, 2.5 to < 5 cm; and grade 3, ≥ 5 cm. The extent of injection site pain was graded as grade 1, easily tolerated; grade 2, discomfort interferes with normal activities; and grade 3, unable to perform normal activities. The extent of fever was measured as grade 1, ≥ 37.5 to < 38.0°C; grade 2, ≥ 38.0 to < 39.0°C; and grade 3, ≥ 39.0°C. Extent of headache, malaise, and myalgia was measured as grade 1, noticeable but does not interfere with daily activities; grade 2, interferes with daily activities; and grade 3, prevents daily activities. Results are based on the number of vaccinated participants with at least 1 available data point.

study compared to 7 months in the previous study (6). The number of prior doses of MPV has also been demonstrated to affect the serogroup C response to subsequent monovalent serogroup C conjugate (MCC) vaccine. Serogroup CSBA GMTs were shown to be reduced following MCC vaccine in children who had received three prior doses of MPV compared to those who had only received one prior dose of MPV (16).

In the present study, the serogroup C-specific IgG GMCS between the 2 groups did not differ; this reflects the differences between the IgG enzyme-linked immunosorbent assay (ELISA) and the SBA assay. The SBA assay, considered the gold standard for the quantitation of meningococcal antibody responses (5), measures functional antibody against the whole meningococcus strain. Thus, the assay more completely assesses vaccine response and protection, as it detects vaccine-elicited antibodies regardless of isotype. This is opposed to serogroup-specific IgG concentration measurements that only assess capsular polysaccharide-specific IgGs with variable avidity to the ELISA-bound antigen (7). Likewise, although the serogroup A SBA GMCS did not appear much different postvaccination between the two groups, the serogroup A-specific IgG GMCS were higher for those who had received prior MPV4, again reflecting the differences in the two immunoassays. These discordant results between the two assays for serogroup A suggest that prior vaccination had an adverse effect on antcapsular antibody functional activity; that is, on average, twice the concentration of antcapsular serogroup A antibody was needed for complement-mediated lysis in those previously vaccinated than in naïve subjects. For serogroup C, the results suggest that the quality and not the quantity of the response was affected by prior vaccination because the IgG GMCS were similar, but significantly higher SBA GMCS were observed in the naïve group. These differences in serogroup A and C responses in the previously vaccinated group may reflect the differences in these polysaccharide antigens.

Discordant results between serogroup A SBA assay and ELISA results were demonstrated in a study of West African children aged 12 to 23 months who received either a single dose of quadrivalent A, C, Y, and W-135 polysaccharide vaccine or Haemophilus influenzae type b (Hib) conjugate vaccine followed 10 months later by monovalent A conjugate vaccine (21). The serogroup A SBA GMTs 28 days after conjugate vaccine were similar between those who received prior polysaccharide vaccine and those who did not, 6,708.9 (95% CI, 5,097.6 to 8,829.5) and 9,342.9 (95% CI, 7,043.8 to 12,392.4), respectively, but the serogroup A-specific IgG GMCS were higher in those who had received prior polysaccharide treatment (38.1 µg/ml [95% CI, 29.7 to 48.9]) than in those who received the control Hib conjugate vaccine (15.4 µg/ml [95% CI, 11.7 to 20.2]).

The MCV4 safety profiles for the prior-MPSV4 group and the meningococcal vaccine-naive group were similar; a substantial majority of solicited adverse reactions were grade 1 in intensity, while grade 3 reactions were reported only for fever. This is similar to results reported after a single dose of MPSV4 in 2- to 10-year-old children from the United States (20), and the results suggest that the safety of a single dose of the conjugated vaccines is similar to that of the polysaccharide vaccine.

In conclusion, this study has demonstrated that MCV4 vaccine elicited a robust immune response in children who previously received MPSV4. These data support the notion that children in the KSA who have previously received MPSV4 can be vaccinated with MCV4 without further aggravating previously induced hyporesponsiveness. Whether the response in both groups could be equally improved by a further booster of MCV4 would be of interest to our understanding of polysaccharide-induced hyporesponsiveness.

ACKNOWLEDGMENTS

We gratefully acknowledge the dedicated effort of the Saudi field team: Mohamed Hamdy, Mohamed Zakai, Magdi Shahin, Taher Hajaj, and Fahmy Imam. We also thank Sanofi Pasteur employees Florence Coux for operational support, Catherine Bravo for her study coordination efforts, and Robert Lersch for writing and editorial support.

This study was funded by Sanofi Pasteur SA.

We declare the following potential conflicts of interest: M.K. and Y.A.-M. have received assistance to attend scientific meetings from Sanofi Pasteur. R.B., H.F., and H.C. have performed contract research on behalf of the Health Protection Agency (funded by Pfizer, Novartis Vaccines, Baxter Bioscience, GlaxoSmithKline, Sanofi Pasteur, Alexion Pharmaceuticals Inc., and Merck). V.B.C. and D.R.J. are Sanofi Pasteur employees. This study has been registered at ClinicalTrials.gov under accession number NCT00539032.
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