Safety and immunogenicity of two doses of quadrivalent meningococcal conjugate vaccine or one dose of meningococcal group C conjugate vaccine, both administered concomitantly with routine immunization to 12- to 18-month-old children

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OBJECTIVES: To describe the immunogenicity and safety of a two-dose series of a quadrivalent meningococcal (serogroups A, C, Y and W) polysaccharide diphtheria toxoid conjugate vaccine (MenACYW-D) administered to toddlers.

METHODS: Children were randomly assigned (1:1) at study entry to receive MenACYW-D at 12 and 18 months of age (group 1; n=61) or meningococcal group C conjugate vaccine (MCC) at 12 months of age (group 2; n=62). All received routine childhood immunizations. A, C, Y and W antibody titres were measured in group 1 before and one month after the 18-month MenACYW-D vaccination and were measured in group 2 at one and seven months post-MCC vaccination. Antibodies elicited by diphtheria and tetanus toxoids, and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and Haemophilus influenzae b conjugate (DTaP-IPV-Hib) vaccine coadministered at the 18-month vaccination were measured one month later.

RESULTS: At 19 months of age, ≥96% in group 1 achieved protective titres for the four meningococcal serogroups after dose 2; 67% in group 2 exhibited protective titres against serogroup C 28 days after MCC vaccination at 12 months of age, declining to 27% seven months later. DTaP-IPV-Hib elicited high antibody concentrations/titres in groups 1 and 2, consistent with historical values. The safety profiles after each dose generated no unexpected safety signals; no serious adverse events were related to vaccination.

DISCUSSION: A two-dose series of MenACYW-D given concomitantly with a DTaP-IPV-Hib booster dose at 18 months of age demonstrated a good immunogenicity and safety profile. A two-dose series of MenACYW-D can be used as an alternative to one dose of MCC and provides protection against additional serogroups (NCT ID: NCT01359449).

Key Words: Canada; Conjugate; Meningococcal; Quadrivalent; Vaccine

ORIGINAL ARTICLE

Meningococci colonize the nasopharynx of 10% to 20% of healthy adults. Although only a small proportion of carriers develop invasive meningococcal disease (IMD), Neisseria meningitidis is nevertheless responsible for substantial worldwide morbidity and mortality, causing both epidemic and endemic disease. Worldwide incidence varies widely from fewer than one to three cases per million.

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100,000 population in developed nations, to 10 to 25 cases per 100,000 in developing countries (1). The most common clinical presentations are meningococcemia and purulent meningitis, with nearly all clinical disease caused by five meningococcal serogroups: A, B, C, Y and W (formerly W-135 and now W, as per Harrison et al [2] (2,3). Even with appropriate treatment, an overall mortality rate of 7% to 19% has been reported for IMD (4), with approximately 10% to 20% of recovering patients sustaining permanent disability (3,5,6).

In Canada, meningococcal illness has been a notifiable disease since the 1920s (7), with the annual incidence since the 1950s ranging from approximately 0.5 to 2 cases per 100,000 population. Serogroup B accounts for approximately one-half of all current cases, mostly in children and young adults, with remaining cases divided primarily between serogroups C, Y and W. A multicomponent meningococcal B vaccine was licensed in Canada in late 2013 (8).

Provincial vaccination programs against serogroup C were instituted during 2002 to 2005 to deal with outbreak clusters that had arisen in Canada since 1989. Variability in vaccination schedules evolved, such that in 2012, nine of 13 provinces and territories administer a single dose of monovalent serogroup C meningococcal conjugate vaccine (MCC) vaccine at 12 months of age, one province and two territories give one dose of MCC at two and 12 months of age, and one province gives one dose at two, four and 12 months of age. MCC vaccines (serogroup C polysaccharide antigen conjugated to CRM197 protein or tetanus toxoid) are administered throughout Canada, and all provincial jurisdictions administer a booster dose at 10 to <18 years of age of either MCC (seven jurisdictions) or quadrivalent ACWY conjugate vaccine (six jurisdictions) (9). As a result of these programs, the incidence of serogroup C IMD has decreased from 0.6 per 100,000 in 2001 to <0.1 per 100,000 between 2009 and 2011 (10). Since 2007, the incidence of IMD caused by serogroup C has been less than that of serogroup Y.

Although endemic incidence is low in Canada, the potential for outbreaks by any of the four non-B disease-causing serogroups is a concern. Such outbreaks are facilitated by global tourism, in which travellers can introduce more infectious and/or invasive forms of IMD. For example, the annual Hajj pilgrimage has been associated with outbreaks of IMD caused by various serogroups. There was a serogroup A outbreak in the late 1980s controlled with mandatory vaccination. An international outbreak of the previously rare W serogroup in 2000 to 2001 was associated with a new and hypervirulent form of IMD that had a high attack rate and a case fatality rate of 37% (11).

Future outbreak prevention may need to focus on vaccination against all major preventable serogroups and not only serogroup C if such outbreaks in Canada are due to non-B, non-C serogroups. The current study assesses the immunogenicity and safety of a meningococcal B conjugate vaccine (MenACWY-D [Menactra, Sanofi Pasteur, France]) when administered with various vaccines. There was a serogroup A outbreak in the late 1980s controlled with mandatory vaccination. An international outbreak of the previously rare W serogroup in 2000 to 2001 was associated with a new and hypervirulent form of IMD that had a high attack rate and a case fatality rate of 37% (11).

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TABLE 1
Distribution of study participants and demographic characteristics on study entry

| Distribution                          | Group 1 (MenACYW-D) | Group 2 (MCC) |
|---------------------------------------|---------------------|---------------|
| Randomly assigned participants        | 61 (100)            | 62 (100)      |
| Received study vaccine at 12 months   | 60 (96)             | 62 (100)      |
| Received study vaccine at 18 months   | 58 (95)             | NA            |
| Discontinued at any point             |                     |               |
| Voluntary withdrawal                  | 3 (6)               | 2 (2)         |
| Lost to follow-up                     | 1 (1)               | 0 (0)         |
| Protocol noncompliance                | 0 (0)               | 2 (2)         |
| Completed study                       | 57 (93)             | 58 (94)       |
| Full analysis set                     | 55 (90)             | 62 (100)      |
| DTaP-IPV-Hib full analysis set        | 51 (84)             | NA            |
| Safety analysis set                   | 60 (98)             | 62 (100)      |
| **Demographic characteristic**        |                     |               |
| Female sex, %                         | 56                  | 53            |
| Median age, months (minimum, maximum) | 12.4 (12.0, 13.2)   | 12.3 (12.0, 13.1) |

Data presented as n (%) unless otherwise indicated. DTaP-IPV-Hib Diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed); MenACYW-D Quadrivalent meningococcal conjugate vaccine; MCC Meningococcal conjugate group C vaccine; n Values based on all participants available at enrollment; NA Not applicable;

Serogroup A, 96.1% for serogroup C, 100% for serogroup Y and 98% for serogroup W (Table 2). For group 2, protection against serogroup C was approximately 67% one month postvaccination and declined to 26% at seven months postvaccination. This value was similar to the 18-month pre-dose 2 level of group 1 (Table 2).

Antibody concentrations and titres elicited by DTaP-IPV-Hib components did not appear to be adversely affected by MenACYW-D coadministration. The seroprotection rates and booster response rates were generally similar for groups 1 and group 2, although there was a tendency for group 2 to have lower booster response rates (Table 3).

At 18 months of age (six months after receiving the first MenACYW-D dose), GMTs (1/dilution) were 15.8 for serogroup A, 12.1 for serogroup C, 94.2 for serogroup Y and 61.5 for serogroup W (Table 4). One month after dose 2 of MenACYW-D (at 19 months of age), the serogroup C GMT among group 1 children was 957 (95% CI 594 to 1540). For other serogroups, the GMT responses were of a similar or higher magnitude. In contrast, one month after MCC vaccination, the GMT was 71 (95% CI 39.3 to 128) and seven months after MCC vaccination, the serogroup C GMT had declined to 11 (95% CI 6.8 to 18.1), similar to the GMTs pre-dose 2 for the MenACYW-D group. Dose 2 MenACYW-D GMTs against other serogroups were higher among group 1 vaccines than among those in group 2 at the same time assessment (A: 1740 versus 4.4; Y: 719 versus 31.3; W: 970 versus 5.3). MCC did not contain antigens against these serogroups (Tables 2 and 4).

Safety data
Table 5 summarizes the safety profile for each group and dose. Injection site reactions tended to be reported more frequently after dose 2 of MenACYW-D, while systemic solicited reactions were similar for both doses of MenACYW-D and in both groups (Figure 1). Redness and tenderness were the most commonly reported injection-site reactions, whereas irritability was the most frequently reported solicited systemic reaction. Grade 3 reactions were uncommon, and the most frequently observed grade 3 solicited reactions were fever (5.2%), irritability (3.4%) and tenderness (3.4%) (Figure 1).

Three serious adverse events were reported, and none were considered to be vaccination-related by investigators (febrile convulsion...
in group 1 106 days after dose 1 of MenACYW-D, PCV13 and MMRV vaccines; bronchiolitis in group 2 188 days after MCC, PCV13 and MMRV doses, and 14 days after the DTaP-IPV-Hib and MMR doses; rickets in group 2 126 days after MCC, PCV13 and MMRV doses). There were no deaths during the study, and all participants completed the trial.

DISCUSSION

The present study described the safety and immunogenicity of MenACYW-D administered at 12 and 18 months of age versus a single dose of MCC at 12 months of age, both coadministered with routine childhood vaccinations. Current immunization programs in Canada use quadrivalent meningococcal conjugate vaccines or MCC vaccines.
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for adolescents and MCC for infants up to 12 months of age. Routine use of quadrivalent meningococcal conjugate vaccine in toddlers could expand protection against IMD caused by A, C, Y and W serogroups; this could lead to expanded meningococcal disease prevention throughout childhood. The study results demonstrate that MenACYW-D has a good immunogenicity and safety profile, and can be used as an alternative to MCC in Canadian vaccination programs. In particular, we found that the second dose of MenACYW-D resulted in higher seroprotection rates against four serogroups and potentially better protected toddlers from IMD. In the other study arm, serogroup C seroprotection rates had declined to 26% seven months after a single dose of MCC vaccine, similar to the seroprotection rate for serogroup C six months after the first dose of MenACYW-D.

A second study objective was to describe the immunogenicity of components of routine combination vaccines administered at 12 and 18 months age when administered concurrently with MenACYW-D. Antibody responses to all DTP-IPV-Hib antigens were generally similar for both groups. Furthermore, these immunogenicity results were similar to those of a historical control (Table 5) (15). Therefore, a clinically important interference between MenACYW-D and DTP-IPV-Hib at 18 months of age is unlikely.

One limitation of the present study is that antibody responses and interactions among MenACYW-D, PCV13 and MMRV at the 12-month dose, and between MenACYW-D and MMR at the 18-month dose were not examined. Such comparisons were not possible because of the limited blood volume and frequency of collection. However, Pina et al (14) found no negative interference when MenACYW-D was administered as a second dose at 12 months of age with MMRV. When PCV7 was coadministered with MenACYW-D, >98% of recipients achieved seroprotection to all vaccine serogroups, although GMTs tended to be lower (14).

Data regarding duration of the antibody responses after a two-dose series of MenACYW-D are not available for the 12- and 18-month two-dose schedule. Similarly, the potential for a booster effect has yet to be evaluated among adolescents who received a quadrivalent conjugate vaccine in early childhood.

The safety profiles of both schedules were good and generally similar. While some injection site and systemic reactions were more frequently reported in group 1 than in group 2, grade 3 reactions were infrequent and there were no withdrawals as a result of safety concerns.

Overall, a two-dose schedule of MenACYW-D resulted in higher bactericidal antibody responses at 19 months of age against serogroup C than one MCC dose alone (Table 4) and also provided high responses against serogroups A, Y and W.

Data describing MenACYW-D use in infant and toddlers first began to appear in 2006 (16) and more fully in Pina et al (14) in 2012. The data presented in the present study extend and confirm the findings of these previous studies. Our data indicate that a 12- and 18-month schedule may be an alternative to MCC at 12 months of age when administered concurrently with MenACYW-D. Antibody responses to all DTaP-IPV-Hib antigens were generally similar for both groups. Furthermore, these immunogenicity results were similar to those of a historical control (Table 5) (15). Therefore, a clinically important interference between MenACYW-D and DTP-IPV-Hib at 18 months of age is unlikely.

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