SAFETY AND IMMUNOGENICITY OF A 2-DOSE SCHEDULE (12 MONTHS AND 18 MONTHS OF AGE) OF A QUADRIVALENT MENINGOCOCCAL POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE

F. Noya,[1] D. McCormack,[1] D.L. Reynolds,[2] D. Neame,[3] P. Oster[4]

[1]McGill University Health Centre, Montreal, QC, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Sanofi Pasteur Ltd., Toronto, ON, Canada; [4]Sanofi Pasteur, Lyon, France

BACKGROUND

- The endemic incidence of meningococcal illness in Canada is low, although the potential for outbreaks remains
- Monovalent serogroup C meningococcal conjugate vaccine (MCC) has been provided in Quebec, Canada since 2001
- The incidence of serogroup Y is approximately equal to that of C, while A and W-135 are lower[1]
  - With the facilitation of international travel, any serogroup could cause outbreaks, thus prevention should focus on vaccination against all major serogroups
- In Canada, meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MenACYW-D) was licensed in 2006 for administration to children, adolescents, and adults aged 2 through 55 years[2]
- A 2-dose schedule of MenACYW-D, administered 3 months apart, was approved in Canada in 2012 for children 9 through 23 months of age[3]
- A 2-dose schedule of MenACYW-D in children aged 12 and 18 months would fit current Quebec programs and would improve coverage against 4 major meningococcal serogroups

STUDY ENDPOINTS

PRIMARY

- Describe the immunogenicity of MenACYW-D administered concomitantly with routine immunizations to meningococcal vaccine-naïve participants at 12 and 18 months of age (measured by serum bactericidal assay using baby rabbit complement [SBA-BR])
- Describe the immunogenicity of MCC administered concomitantly with routine immunizations at 12 months of age (measured by SBA-BR)

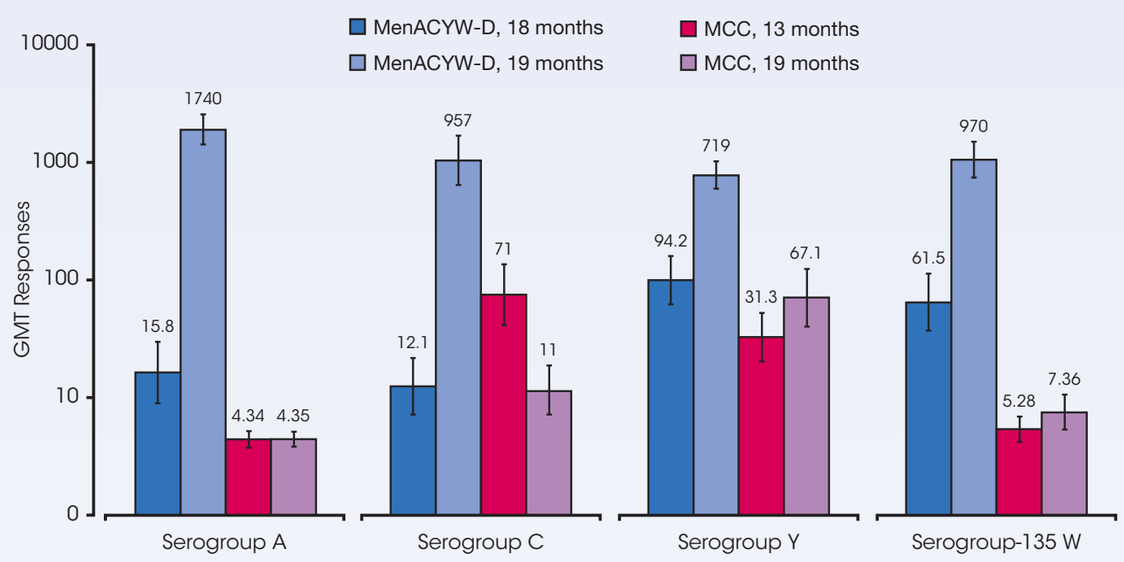
SECONDARY

- Describe the safety profile of MenACYW-D and MCC vaccines given concomitantly with routine immunization
- Describe the immunogenicity of DTaP-IPV-Hib coadministered with MenACYW–D at 18 months

METHODS

- A phase IIIb, randomized, open-label, single-center, descriptive trial examined the immunogenicity and safety at 19 months of age of MenACYW-D administered to children in a 2-dose series (12 and 18 months) or standard serogroup C conjugate vaccine (MCC) administered at 12 months (ClinicalTrials.gov Identifier: NCT01359449)
- Key inclusion criteria included:
  - Healthy, full-term children ≥12 months old (365–400 days)
- Key exclusion criteria included:
  - Previous meningococcal vaccination
  - Current illness, risk factor, or administrative complication (eg, scheduled participation in another trial) that could negatively impact trial validity or child health
- Full inclusion/exclusion information are available at ClinicalTrials.gov[4]
- The study was approved by the appropriate ethics committee, and was in accord with the Declaration of Helsinki, Good Clinical Practice, the Tri-Council Policy Statement, and applicable International Conference on Harmonization guidelines
- Participants in the MenACYW-D Group received a 2-dose series of MenACYW-D at ages 12 months (range 365–400 days) and 18 months (range 519–579 days) (Figure 1)
- Participants in the MCC Group received 1 dose of MCC at age 12 months (range 365–400 days)
- Other vaccinations in both groups followed Quebec guidelines, including measles, mumps, rubella, and varicella (MMRV) vaccine and pneumococcal conjugate vaccine (PCV13) at 12 months, and MMR and diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, and polio (DTaP-IPV-Hib) vaccine at 18 months and influenza vaccine in the fall of 2011
- Blood samples were collected at ages 18 and 19 months (pre-Dose 2 and 1 month post-Dose 2, respectively) for the MenACYW-D Group and in the MCC Group at ages 13 and 19 months (1 and 7 months post-dose, respectively) (Figure 1)

Figure 1. Anti-Meningococcal Antibody GMT Responses to Serogroups A, C, Y, and W-135 (Full Analysis Set)



- Global Clinical Immunology, Sanofi Pasteur, Swiftwater, PA, USA assessed the elicited responses[5]
  - Functional antibody activity of anti-meningococcal antibodies to serogroups A, C, W-135, and Y was measured by serum bactericidal assay with baby rabbit complement (SBA-BR)
    - Serogroup seroprotection was defined an SBA-BR titer ≥1:8 (1/dil)
  - Anti-diphtheria antibodies and anti-poliovirus types 1, 2, and 3 antibodies were measured by functional assays
    - Diphtheria seroprotection was defined as a serum antitoxin level ≥0.1 IU/mL and polio as a neutralizing antibody titer ≥1:8 (1/dil)
  - Anti-tetanus antibodies, anti-*H. influenzae* type b (anti-polyribosylribitol phosphate [PRP]) antibodies, and anti-pertussis antibodies (pertussis toxin [PT], pertactin [PRN], filamentous hemagglutinin [FHA], and fimbriae types 2 and 3 [FIM]) concentrations were measured by antibody binding assays
    - Tetanus seroprotection rates were defined using a serum antitoxin level ≥0.1 IU/mL, *H. influenzae* type b seroprotection rates as an anti-PRP antibody titer ≥1.0 µg/mL
    - Anti-pertussis booster response was a 4-fold antibody concentration increase where pre-dose titers were <4 x lower limit of quantitation (LLoQ) or a 2-fold rise where pre-dose titers were ≥4 x LLoQ
- Serious adverse events (SAEs), solicited injection site and systemic reactions, and unsolicited adverse events (AEs) were recorded
  - The 95% confidence intervals (CI) were calculated by accepted methods
  - The full analysis set included all participants receiving ≥1 dose of study or control vaccine; the safety analysis set includes all participants who reported safety data

RESULTS

PARTICIPANTS

- Healthy children (N=123) were randomized to the MenACYW-D Group (n=61) or the MCC Group (n=62)
- Participant baseline demographics of the 2 groups were similar (Table 1)

Table 1. Baseline Demographic Characteristics

	MenACYW-D Group (n = 61)	MCC Group (n = 62)
Female, n (%)	34 (55.7)	33 (53.2)
Age (months)		
Mean (SD)	12.4 (0.3)	12.4 (0.3)
Minimum, maximum	12.0, 13.2	12.0, 13.1

  - Most participants were white: 87% for the MenACYW-D Group and 74% for the MCC Group. The second most represented ethnic group was Other: 6% MenACYW-D and 15% MCC

IMMUNOGENICITY

Immune responses to MenACWY-D and MCC

- Most MenACYW-D Group participants achieved a protective SBA-BR titer for serogroups A (100%), C (96%), Y (100%), and W-135 (98%) 1 month after Dose 2 (Table 2)
  - At 18 months, 6 months after the first MenACYW-D dose, protective SBA-BR titers were 34.6% for serogroup A, 26.9% for C, 82.7% for Y , and 71.2% for W-135 compared to after the second dose (Table 2)
  - In the MCC Group, 67% of participants achieved a protective SBA-BR titer for serogroup C 1 month post-vaccination, declining to 26% at 7 months post-vaccination (Table 2, Figure 1)

Table 2. Percent Participants With SBA-BR Titers ≥1:8 (1/dil) by Serogroup and Age (Full Analysis Set)

		SBA-BR Titers, % (95% CI)	
Serogroup	Age (months)	MenACYW-D Group (n = 55)	MCC Group (n = 62)
A	13	NA	1.7 (0.04; 8.94)
	18	34.6 (22.0; 49.1)	NA
	19	100.0 (93.0; 100)	3.4 (0.42; 11.9)
C	13	NA	66.7 (53.3; 78.3)
	18	26.9 (15.6; 41.0)	NA
	19	96.1 (86.5; 99.5)	25.9 (15.3; 39.0)
Y	13	NA	60.0 (46.5; 72.4)
	18	82.7 (69.7; 91.8)	NA
	19	100.0 (93.0; 100)	67.2 (53.7; 79.0)
W-135	13	NA	8.3 (2.8; 18.4)
	18	71.2 (56.9; 82.9)	NA
	19	98.0 (89.6; 100)	19.0 (9.9; 31.4)

NA, not applicable.

- In the MenACYW-D Group, geometric means titers (GMT) for all serogroups were high at 19 months of age ranging from 719 to 1740 after the second vaccine dose (Figure 1) and had increased from the 18 months pre-Dose 2 vaccination GMTs of 12 to 94
- The GMTs for serogroup C in the MCC group were 71 after 13 months and 11 after 19 months
- In the MCC Group, serogroup Y had relatively high baseline titers at 13 months (31.3) and 19 months (67.1), although serogroup Y polysaccharides were not in MCC vaccine (Figure 1)

Immune responses to DTaP-IPV-Hib vaccine

- Seroprotection rates elicited by diphtheria, tetanus, and PRP antigens were 100% in the MenACWY-D and MCC Groups (Table 3)
- 100% of participants achieved seroprotection against polio types 1, 2, and 3
- The pertussis booster response rates in the MenACYW-D Group tended to be higher than the MCC Group (Table 3)
  - Pertussis GMTs in the MenACYW-D Group were >120 EU/mL for all antigens

Table 3. Seroprotection/Booster Response to Diphtheria, Tetanus, H. Influenzae Type b (PRP), and Pertussis Antigens at 19 Months of Age, % (95% CI)

	MenACYW-D Group (n = 51)	MCC Group (n = 61)
Diphtheria, ≥0.1 IU/mL	100.0 (92.3; 100)	100.0 (93.4; 100)
Tetanus, ≥0.1 IU/mL	100.0 (92.5; 100)	100.0 (93.3; 100)
PRP; ≥1.0 µg/mL	100.0 (92.3; 100)	100.0 (93.3; 100)
Pertussis ; EU/mL		
PT	100.0 (92.0; 100)	94.3 (84.3; 98.8)
PRN	92.7 (80.1; 98.5)	78.0 (65.3; 88.9)
FHA	97.7 (88.0; 99.9)	88.0 (75.7; 95.5)
FIM	100.0 (91.6; 100)	95.8 (85.7; 99.5)

PRP = polyribosyl ribitol-phosphate; PT = pertussis toxin; PRN = pertactin; FHA = filamentous hemagglutinin; FIM = fimbriae type 2 and 3

SAFETY AND TOLERABILITY

- Both vaccines were generally well tolerated (Table 4)

Table 4. Safety Assessments (Safety Analysis Set); n (%)

Participants Experiencing ≤1:	MenACYW-D Group (n = 60)	MCC Group (n = 62)
Solicited injection site reaction	48 (80.0)	33 (55.0)
Solicited systemic reaction	59 (98.3)	48 (80.0)
Unsolicited non-serious injection site AR	1 (1.7)	1 (1.6)
Unsolicited non-serious systemic AE	50 (83.3)	37 (59.7)
Unsolicited non-serious systemic AR	2 (3.3)	2 (3.2)
AE leading to study discontinuation	0 (0.0)	0 (0.0)
SAE	1 (1.7)	2 (3.2)

AE = adverse event; AR = adverse reaction; SAE = serious AE

- More solicited reactions were reported in the MenACYW-D Group, but 2 doses of MenACYW-D were administered compared to 1 dose in the MCC Group
  - Unsolicited non-serious injection site and systemic adverse reactions (AR) were similar in the 2 groups
- Three SAEs were reported (1 febrile convulsion in the MenACYW-D Group; 1 bronchiolitis and 1 rickets in the MCC Group) and were not vaccination-related
- No participants withdrew from the study due to adverse events

CONCLUSIONS

- 2 doses of MenACYW-D resulted in higher serogroup C immune responses at 19 months of age than a single dose of MCC
- MenACYW-D administered as a 2-dose series, concomitantly with a booster dose of DTaP-IPV-Hib at 18 months of age, demonstrated good immunogenicity and safety profile
- MenACYW-D can be used as an alternative to MCC in vaccination programs

DISCLOSURES

The Research Institute of the McGill University Health Centre received funding from Sanofi (held in an account under F. Noya) to conduct this study. F. Noya received an honorarium and travel expenses. Dr Noya has received travel grants from Merck and has also received other research grants from Sanofi Pasteur and Merck. D. McCormack was the site coordinator for this study. D.L. Reynolds was an employee of Sanofi Pasteur when the study was designed and is currently an adjunct professor at the University of Toronto. D. Neame and P. Oster are full-time employees of Sanofi Pasteur.

ACKNOWLEDGMENTS

This study was funded by Sanofi Pasteur. Editorial support was provided by Robert Lersch, PhD of Sanofi Pasteur and Shelley Maria Lindley, PhD of PAREXEL and funded by Sanofi Pasteur.

REFERENCES

1. Bettinger J, Scheifele D, Le Saux N, Halperin S, Vaudry W, Bortolussi R, Tsang R. Update on the incidence of meningococcal invasive infections in Canada, IMPACT 2002-2009. Presented at 17th International Pathogenic Neisseria Conference, September 11-16th, 2010; Banff, Alberta. Poster P036.
2. National Advisory Committee on Immunization (NACI). An update on the invasive meningococcal disease and meningococcal vaccine conjugate recommendations. An Advisory Committee Statement (ACS). *Can Commun Dis Rep* 2009;35(ACS-3):1-40.
3. Menactra® [product monograph]. Toronto, Ontario, Canada: Sanofi Pasteur Limited; 2012. https://www.vaccineshoppecanada.com/document.cfm?file=menactra_e.pdf. Accessed September 10, 2012.
4. U.S. National Institutes of Health (NIH). Study of two doses of Menactra® or one dose of monovalent meningococcal Group C vaccine with routine immunizations. http://clinicaltrials.gov/ct2/show/NCT01359449?term=MTA73&rank=1. Accessed September 10, 2013.
5. Pina LM, Bassily E, Machmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria-toxoid-conjugate vaccine in infants and toddlers: 3 multicenter, phase III studies. *Pediatr Infect Dis J* 2012;31:1173-183.

Presented at the Meningitis Research Foundation (MRF) 2013 International Conference, 5-6 November 2013, London, UK.

SANOFI PASTEUR