Profile of serogroup Y meningococcal infections in Canada: Implications for vaccine selection

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Canada is a leader in establishing routine infant immunization programs against meningococcal C disease. Currently, all provinces have routine programs to provide meningococcal C conjugate vaccines to infants and children. The result of the existing programs has been a decrease in serogroup C incidence. The second most common vaccine-preventable serogroup in Canada is serogroup Y, the incidence of which has been stable. The availability of a quadrivalent conjugate vaccine against serogroups A, C, Y and W135 focuses attention on serogroup Y disease as it becomes relatively more prominent as a cause of vaccine-preventable invasive meningococcal disease. This vaccine was licensed in November 2006 but is not routinely used except in Nunavut, New Brunswick and Prince Edward Island. To allow a better understanding of the 'value added' by a serogroup Y-containing vaccine, it is necessary to have a contemporary profile of Y disease in Canada. In the present paper, recent surveillance data on invasive meningococcal disease across Canada are summarized.

Key Words: *Invasive meningococcal disease; Meningococcal vaccine; Morbidity; Mortality;* Neisseria meningitides; *Serogroups A, C, Y, W135*

Le profil des infections à méningocoque de sérogroupe Y au Canada : Les conséquences sur la sélection des vaccins

Le Canada est un chef de file dans la mise en œuvre de programmes systématiques de vaccination des enfants contre la maladie à méningocoque de sérogroupe C. Toutes les provinces sont dotées de programmes systématiques pour administrer le vaccin conjugué contre le méningocoque de sérogroupe C aux nourrissons et aux enfants. Grâce à ces programmes, l'incidence du sérogroupe C a diminué. Le deuxième sérogroupe évitable par un vaccin en importance au Canada est le sérogroupe Y, dont l'incidence est stable. La disponibilité d'un vaccin conjugué quadrivalent contre les sérogroupes A, C, Y et W135 fixe l'attention sur la maladie à sérogroupe Y, qui devient relativement plus dominante comme cause de maladie à méningocoque envahissante évitable par un vaccin. Ce vaccin a été homologué en novembre 2006, mais il n'est pas utilisé systématiquement, sauf au Nunavut, au Nouveau-Brunswick et à l'Île-du-Prince-Édouard. Afin de mieux comprendre la « valeur ajoutée » d'un vaccin contenant le sérogroupe Y, il est nécessaire de disposer d'un profil contemporain de la maladie à sérogroupe Y au Canada. Dans le présent article, on résume les récentes données de surveillance sur la maladie à méningocoque envahissante au Canada.

Canada is a leader in establishing routine infant immunization programs against meningococcal C disease. Currently, all provinces have routine programs to provide meningococcal C conjugate (MenC) vaccines to infants and children. The motivation for these programs included the cyclical occurrence of serogroup C epidemics, unpredictable hyperendemic disease in some areas, the circulation of a hypervirulent serogroup C strain and relatively high disease incidence in infants and young children (1-6) The result of the existing programs has been a decrease in serogroup C incidence (7). The second most common vaccine-preventable serogroup in Canada is serogroup Y, the incidence of which has been stable (7,8).

The availability of a quadrivalent conjugate vaccine against serogroups A, C, Y and W135 focuses attention on serogroup Y disease as it becomes relatively more prominent as a cause of vaccine-preventable invasive meningococcal disease. This vaccine was licensed in November 2006 but is not routinely used except in Nunavut, New Brunswick and Prince Edward Island. To allow a better understanding of the 'value added' by a serogroup Y-containing vaccine, it is necessary to have a contemporary profile of serogroup Y disease in Canada. We have summarized recent surveillance data on invasive meningococcal disease across Canada.

METHODS

From 2002 to 2007, active, metropolitan area surveillance for adult and pediatric hospital admissions related to infection with *Neisseria meningitidis* was conducted by the 12 centres of the Canadian Immunization Monitoring Program, Active (IMPACT), in collaboration with local public health officials. IMPACT is a national surveillance initiative with centres located in pediatric tertiary care centres in Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Saskatchewan, Alberta and British Columbia. All local and referred cases seen at an IMPACT hospital were reported. In addition to cases admitted to IMPACT centres, each IMPACT centre identified a geographic area with a defined population base and captured all hospitalized cases occurring in children and adults residing

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within this defined area. Surveillance included over 16 million Canadians, or just over 50% of the Canadian population. Ethics approval was obtained at all hospitals.

All centres used the same case finding strategies, case definition and report form to abstract information from the patient's chart. Patients were not directly contacted. Information on the case report form included the patient's age, sex, prior health, including any pre-existing medical conditions, presenting manifestations, the clinical presentation of the current meningococcal infection, the sources of positive cultures, level of care required, outcome and complications or sequelae. Presenting manifestations included signs of bacteremia (with and without diagnosed septic shock), meningitis, pneumonia, pericarditis, arthritis, endophthalmitis, seizure, petechial rash, ecchymosis and skin necrosis. Charts were reviewed after hospital discharge to capture data on sequelae at discharge. Sequelae included amputation, scarring, renal dysfunction, deafness, seizures requiring anticonvulsants on discharge and other neurological deficits. Meningitis as a presenting manifestation was defined as having either a positive culture from cerebrospinal fluid (CSF); detection of nucleic acid from *N meningitidis* by polymerase chain reaction (PCR) from CSF; or positive blood culture with CSF pleocytosis (white blood cell count greater than 10×10^6/L).

Inclusion as a case of invasive meningococcal disease required isolation of *N meningitidis* from a sterile site (eg, blood, CSF, joint, pleural, peritoneal or pericardial fluid), or a positive PCR test from blood or CSF. Isolates were forwarded to the National Microbiology Laboratory in Winnipeg, Manitoba, for further characterization and confirmation of serogroup. The latter data were used when available; otherwise, locally determined serogroup data were used. For the present analysis the focus was on vaccine-preventable cases caused by serogroups C and Y. Cases caused by serogroup A and W135 were few and are briefly described. Cases caused by serogroup B or other serogroups were excluded because these are not currently preventable by licensed vaccines in Canada. Three separate multivariate logistic regression models were used to determine differences between serogroups C and Y, and predictors for morbidity and mortality among all four vaccine-preventable serogroups (A, C, Y and W135). Characteristics examined in univariate regression were age, sex, pre-existing underlying health condition, manifestations (bacteremia, meningitis or both), septic shock, intensive care unit stay, sequelae and death. Characteristics with a P≤0.05 were considered significant and included in the final model. SAS version 9.1.3 (SAS Institute, USA) was used for all analyses.

RESULTS

In total, 227 meningococcal cases caused by vaccine-preventable serogroups A, C, Y and W135 were identified during six years of active surveillance. Two hundred seventy-two serogroup B cases, one nonencapsulated mutant (9), 11 cases identified by PCR without serogrouping, and three isolates that were not available for serogrouping were excluded from the analysis. Two serogroup A cases occurred in adults with recent travel history to India and Pakistan, respectively, and appear to be imported cases. Characteristics of the cases caused by serogroups C, Y and W135 are shown in Table 1. The median age of cases was 18.5 years with a range of zero to 95 years. The most common presenting manifestations included signs of bacteremia (51%), signs and symptoms of meningitis (18%), or signs of both bacteremia and meningitis (26%). Additional laboratory features by age for cases with serogroups C and Y are shown in Table 2. For the W135 cases (not shown in Table 2), diagnosis was made entirely by positive culture of blood (15 of 20) or CSF (seven of 20); seven of 20 (35%) had associated thrombocytopenia and one had leukopenia.

TABLE 1
Characteristics of cases of serogroup C, Y and W135 infection, 2002 to 2007

	Serogroup			
Characteristics	C, n=122	Y, n=83	W135, n=20	Total, n=227*
Age group, years				
<2	4 (3)	7 (8)	7 (35)	18 (8)
2–19	33 (27)	28 (34)	7 (35)	68 (30)
20–59	72 (59)	22 (27)	4 (20)	99 (44)
≥60†	13 (11)	26 (31)	2 (10)	42 (19)
Male	66 (54)	39 (47)	10 (50)	116 (51)
Underlying health condition†	34 (28)	47 (57)	9 (45)	90 (40)
Immunocompromised	5 (4)	8 (10)	1 (5)	14 (6)
Presenting manifestation				
Bacteremia	53 (43)	55 (66)	7 (35)	116 (51)
Meningitis	23 (18.9)	12 (15)	5 (25)	40 (18)
Bacteremia/meningitis†	43 (35)	9 (11)	5 (25)	58 (26)
Other manifestation	3 (3)	7 (8)	3 (15)	13 (6)
Septic shock†	59 (48)	10 (12)	3 (15)	73 (32)
Mean days in hospital (range)	14.4 (1–272)	10.7 (1–91)	10.0 (1–53)	12.6 (1–272)
ICU care†	87 (71)	30 (36)	7 (35)	126 (56)
Days in ICU, mean (range)	5.8 (1–36)	4.3 (1–11)	4.0 (1–18)	5.4 (1–36)
Death from infection†	16 (13)	2 (2.4)	1 (5)	20 (8.8)
Sequelae†	28 (23)	7 (8)	2 (10)	37 (16)

*Data presented as n (%) unless otherwise specified. *Total includes two serogroup A cases; †Significant difference (P≤0.05) in univariate regression between serogroup C and serogroup Y. ICU Intensive care unit*

Differences between serogroup Y and C

Serogroup Y was significantly more likely to occur in adults 60 years of age and older (odds ratio [OR] 3.82, 95% CI 1.83 to 8.01) and in cases with underlying medical conditions (OR 3.38, 95% CI 1.88 to 6.1) when compared with serogroup C. After adjusting for age and underlying health conditions, cases with serogroup Y infection were significantly less likely to have septic shock (OR 0.20, 95% CI 0.08 to 0.48), less likely to require intensive care (OR 0.50, 95% CI 0.14 to 1.0), less likely to die (OR 0.11, 95% CI 0.02 to 0.52) and less likely to suffer significant sequelae (OR 0.28, 95% CI 0.11 to 0.69) than those with serogroup C. Finally, as shown in Table 2, the clinical manifestations and laboratory features of serogroup Y were less severe than those of serogroup C.

Predictors for death

Of the 20 deaths, two occurred in children two to five years of age, two in adolescents 18 to 19 years of age and 16 in adults 20 years of age and older (eight in adults 20 to 49 years of age). In adults, 13 deaths (81%) were caused by serogroup C, two by

TABLE 2
Selected clinical and laboratory features for invasive disease due to serogroups C and Y by age

Serogroup and age	Positive blood culture	Positive CSF culture	PCR positive	Other sterile site culture*	CSF pleocytosis†	Abnormal INR‡	Abnormal platelets	WBC <5×10^9/L
Serogroup C, n=122 (%)	92 (75)	37 (30)	20 (16)	3 (3)	60/75 (80)	82/108 (76)	75 (62)	13 (11)
Age, years								
<2, n=4	3 (75)	1 (25)	0	0	3/3 (100)	3/3 (100)	2 (50)	1 (25)
2–19, n=33	25 (76)	10 (30)	6 (18)	0	18/24 (75)	23/31 (74)	18 (55)	3 (9)
20–59, n=72	53 (74)	24 (33)	14 (19)	2 (3)	34/42 (81)	47/63 (75)	47 (65)	9 (11)
≥60, n=13	11 (85)	2 (15)	0	1 (8)	5/6 (83)	9/11 (82)	8 (62)	0
Serogroup Y n=83 (%)	68 (82)	16 (19)	4 (5)	4 (5)	20/31 (65)	25/42 (60)	27 (33)	7 (8)
Age, years								
<2, n=7	5 (71)	4 (57)	1 (14)	0	5/7 (71)	1/1 (100)	4 (57)	1 (17)
2–19, n=28	20 (71)	6 (21)	3 (11)	2 (7)	9/12 (75)	12/14 (86)	9 (32)	4 (14)
20–59, n=22	18 (82)	4 (18)	0	2 (4)	4/6 (67)	6/13 (46)	6 (27)	1 (5)
≥60, n=26	25 (96)	2 (8)	0	0	2/6 (33)	6/14 (43)	8 (31)	1 (4)

*Percentage is calculated based on number in each age group within each serogroup, unless otherwise stated. *Other sterile sites include joint fluid (n=6), skin biopsy (n=1) and vitreous fluid (n=1); †Cerebrospinal fluid (CSF) examined for n=106 (52%) and abnormal white blood cells (WBC) for n=80 (number abnormal/total number done); ‡International normalized ratio (INR) examined in n=150 (73%) (number abnormal/total number done). PCR Polymerase chain reaction*

TABLE 3
Type of sequelae due to serogroups C and Y by age

Serogroup and age	Amputation	Skin scarring	Renal dysfunction	Deafness	Seizures*	Neurological sequelae
Serogroup C, n=28 (%)	9 (32)	9 (31)	8 (28)	6 (21)	4 (14)	8 (29)
Age, years						
<2, n=3	1 (33)	1 (33)	1 (33)	1 (33)	1 (33)	1 (33)
2–19, n=9	5 (56)	4 (44)	2 (22)	2 (22)	0	2 (22)
20–59, n=12	3 (19)	3 (25)	4 (33)	2 (17)	2 (17)	5 (31)
≥60, n=4	0	1 (25)	1 (25)	1 (25)	1 (25)	0
Serogroup Y, n=7 (%)	1 (14)	2 (29)	2 (29)	1 (14)	0	0
Age, years						
<2, n=1	0	0	0	1 (100)	0	0
2-19, n=4	1 (25)	2 (50)	1 (25)	0	0	0
20-59, n=2†	0	0	1 (50)	0	0	0
≥60, n=0	0	0	0	0	0	0

**Seizures requiring anticonvulsants on discharge; †One patient had a cataract resulting from serogroup Y infection*

serogroup Y and one by serogroup A. In children and adolescents, three deaths were caused by serogroup C and one by serogroup W135. Adults were more likely to die from meningococcal infection than children (OR 1.59, 95% CI 1.05 to 2.40), regardless of serogroup. Cases infected with serogroup C were more likely to die, regardless of age (OR 4.5, 95% CI 1.4 to 14.5) when compared with serogroups A, Y and W135. Seventeen (7.5%) cases had a history of receipt of antibiotics not related to treatment of meningococcal infection before admission, and all survived.

Sequelae

A total of 37 (16.3%) patients suffered sequelae related to their infection, described in Table 3. The two W135 cases with sequelae (not shown in the table) occurred in children younger than two years of age: one suffered severe unilateral deafness and one had central hypotonia, visual loss and pituitary insufficiency. Of the serogroup C and Y cases with renal dysfunction, four serogroup C cases (three adults and one child) were dialysis dependent, while no serogroup Y case was. Serogroup C caused severe, bilateral deafness in three cases and mild bilateral deafness in three cases, while serogroup Y caused mild, bilateral deafness in one case. Severe central nervous system sequelae caused by serogroup C occurred in six cases, including hydrocephalus (two cases), focal cerebral ischemia (two cases), visual loss (one case) and a third cranial nerve palsy (one case). Three other patients had other persistent significant neurological sequelae manifesting as extremity numbness, tremors and significant weakness. No such sequelae followed serogroup Y infections. Among the eight serogroup C patients with neurological sequelae, no differences were found in presenting manifestations (two with bacteremia, three with meningitis and three with both bacteremia and meningitis) or the occurrence of septic shock (four of eight).

Predictors for sequelae

Multivariate logistic regression showed children younger than two years of age were significantly more likely to suffer from sequelae than older children and adults (OR 7.2, 95% CI 2.0 to 25.5) regardless of causative serogroup. Children ages two to 19 years of age were more likely than adults to suffer from sequelae (OR 2.0, 95% CI 0.87 to 4.4). Cases infected with serogroup C who survived were also significantly more likely to have sequelae, regardless of age (OR 4.8, 95% CI 1.9 to 11.8).

DISCUSSION

The strengths of the IMPACT meningococcal surveillance data are its contemporary nature (current through 2007), national scope, active, population-based case finding, and linked clinical and microbiological data. Moreover, it provides a detailed picture of serogroup A, Y and W135 disease that is unmodified by quadrivalent conjugate vaccine use. An assessment of morbidity and mortality caused by these vaccine-preventable invasive meningococcal serogroups is therefore timely, especially for immunization program planners and health economists.

Significant epidemiological and clinical differences exist between serogroup Y and C disease. Although serogroup C incidence has shown a significant decrease over the past five years in Canada, serogroup Y incidence has remained relatively constant with an average annual incidence per 100,000 of 0.14 (95% CI 0.09 to 0.20) in children younger than 20 years of age and 0.09 (95% CI 0.06 to 0.11) in adults and has not thus far exhibited signs of serogroup replacement (7). Stable serogroup Y incidence has also been shown in the United Kingdom, which started routine infant conjugate C immunization programs in 2000 (10). Whereas in the United States, serogroup Y incidence increased significantly in the 1990's, before conjugated vaccines for meningococcal disease were available, as a result of the sequential emergence of two clonal groups attributable to antigenic shifts (11-15).

In the present series, serogroup Y disease was significantly more likely to occur in adults older than 60 years of age. This is consistent with previous Canadian data from 1999 to 2003, which indicated that the highest percentage of serogroup Y isolates were from adults older than 60 years of age (16). Two large case series of serogroup Y disease from the United States in the period 1992 to 1994 also noted that patients were older compared with non-serogroup Y disease (11,17) This contrasts with recent reports from Colombia that show an increased burden of disease for serogroup Y in children with just 7.5% of the cases in patients 60 years of age and older (18).

We found that disease due to serogroup Y was generally milder than serogroup C disease. Specifically, patients with disease due to serogroup Y were less likely to present in septic shock, have thrombocytopenia or require intensive care. We observed 2.4% mortality among those infected with serogroup Y versus 13% mortality with serogroup C, with mortality most often occurring in adults in both groups. This is consistent with data from others where the case fatality rate for sporadic serogroup C disease was between 11% and 23% whereas the case fatality rate for serogroup Y or W135 has been reported as being between 5% and 9% (11,14,17,19,20).

Although cases infected with serogroup Y were typically older or had underlying medical conditions, they suffered fewer sequelae and in particular, fewer neurological sequelae compared to those infected with serogroup C. Apart from one case of deafness, none of the patients with disease due to serogroup Y had seizures or neurological sequelae. This may be a reflection of less frequent central nervous infection in adults with serogroup Y compared with serogroup C infections (Table 2). Others have noted sequelae rates of 2% to 15% for invasive meningococcal disease, but these rates were not serogroup specific (21-23).

While serogroup Y disease may justify efforts to prevent it through routine vaccination, it is clearly less of a threat than serogroup C disease. The incidence of serogroup Y disease recently in Canada was one-third (35%) of the baseline rate of serogroup C disease (7,8). This fact, along with the milder nature of serogroup Y disease, means that it will be less cost-effective from a public health perspective to prevent such cases through vaccination than was the case for serogroup C disease. However, the cost-benefit ratio will improve if vaccination costs decrease, disease incidence due to serogroups A, Y or W135 increases or virulent clones of these serogroups emerge. The cost-benefit ratio for a quadrivalent vaccine is favourable from an individual perspective, especially for persons at higher risk or those wishing to reduce their risk of invasive meningococcal disease to a minimum. Continued surveillance particularly aimed at monitoring for capsule replacement is essential to understand the effect of vaccination programs on the evolution of meningococcal disease in Canada.

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