

# **The Recommended Use of the Multicomponent Meningococcal B (4CMenB) Vaccine in Canada: *Common Guidance Statement***

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*Prepared by:* Meningococcal B Pilot Project Task Group  
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Recommandations concernant l'utilisation du vaccin multicomposant contre le méningocoque de séro groupe B  
(4CMenB) au Canada : Déclaration *d'orientation commune*

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## List of Abbreviations

4CMenB	Multicomponent meningococcus serogroup B
Agency	Public Health Agency of Canada
CFR	Case fatality ratio
CIRID	Centre for Immunization and Respiratory Infectious Diseases
CI	confidence interval
CIC	Canadian Immunization Committee
CIQ	Comité d'Immunisation du Québec (Quebec Immunization Committee)
CLSC	Local Community Service Centres (Québec)
DPTPHib	diphtheria, tetanus, acellular pertussis, <i>Haemophilus influenzae</i> type b and inactivated poliovirus
DTap-HBV-IPV/Hib	diphtheria, tetanus, acellular pertussis, inactivated polio, <i>Haemophilus influenzae</i> type b and hepatitis B
ELISA	enzyme-linked immunosorbent assay
fHbp	Factor H binding protein
GMC	geometric mean concentration
GMT	Geometric mean titre
GNA	Genome-derived neisserial antigen
hSBA	human complement serum bactericidal activity
IgG	immunoglobulin G
IM	intramuscular
IMD	Invasive meningococcal disease
IMPACT	Immunization Monitoring Program, ACTive
KD	Kawasaki Disease
LL	lower limit
MATS	Meningococcal Antigen Typing
MBPPTG	Meningococcal B Pilot Project Task Group
MCCV-Hib	meningococcal serogroup C and Hib conjugate vaccine
MenACWY-CRM	meningococcal serogroups A, C, W-135 and Y conjugate vaccine
MMR	measles, mumps, rubella vaccine
MMRV	measles, mumps, rubella and varicella vaccine
<i>N. Meningitidis</i>	<i>Neisseria Meningitidis</i>
NACI	National Advisory Committee on Immunization
NHBA	Neisseria heparin-binding antigen
NadA	Neisserial adhesion A
NML	National Microbiology Laboratory
NZ	New Zealand
nCAM	neural cell adhesion molecule
MATS	Meningococcal Antigen Typing System
MLST	Multilocus sequence typing
OMP	Outer membrane protein
OMV	Outer membrane vesicle
PorA	porin A
P/Ts	Provinces and Territories

RCT	Randomized controlled trial
rMenB	Recombinant meningococcal B
SAE	serious adverse event
SD	standard deviation
ST	sequence type

## Introduction

Invasive meningococcal disease (IMD) is an acute and serious disease caused by the bacterium *Neisseria meningitidis*. The most common form of meningococcal infection is the carrier state, in which a person has the bacteria on the mucosal lining of the nose or throat but does not develop symptoms of the disease. A person may remain a carrier of the same strain for as long as six months and remain healthy and asymptomatic. Invasive disease is a severe form of infection that occurs when the bacterium invades into normally sterile sites, such as the bloodstream and the cerebrospinal fluid. IMD most often results in meningitis, or septicemia, or a combination of both. This most usually develops shortly after initial exposure to the organism.

In Canada, four serogroups (B, C, W-135, and Y) are responsible for the majority of meningococcal disease, with incidence varying by the meningococcal serogroup, individual age groups, the geographic area, and the time of year. Since 1993, most cases of infection can be attributed to serogroups B and C.<sup>1</sup> In recent years, the incidence of serogroup C has declined significantly, due to the introduction of meningococcal C conjugate vaccine into routine immunization programs.

Vaccination is the most effective measure for preventing IMD. Previously, the National Advisory Committee on Immunization (NACI) recommended the use of available capsule polysaccharide based vaccines: three monovalent meningococcal conjugate vaccines for serogroup C (Menjugate®, Neis Vac-C® and Meningitec™), two quadrivalent meningococcal conjugate vaccines for serogroups A, C, Y and W-135 (Menactra® and Menveo™) and one quadrivalent polysaccharide meningococcal ACYW-135 vaccine (Menomune®) for the prevention of serogroup A, C, W135 and Y IMD. In March 2013, Health Canada issued a notice of compliance for a new quadrivalent meningococcal conjugate vaccine for serogroups A, C, Y and W-135 (Nimenrix™).

Bexsero® (Novartis Vaccines) is a novel multicomponent meningococcal serogroup B (4CMenB) vaccine. The 4CMenB is the first vaccine that has been created through a process of reverse vaccinology. Through this process potential vaccine targets (i.e. antigens) are identified and developed by sequencing the meningococcal serogroup B genome.<sup>2-4</sup> The vaccine is therefore protective only against the strains that express antigens contained in the vaccine at sufficient levels. A significant proportion, but not all of serogroup B strains express vaccine containing antigens. In addition, antigens contained in the vaccine are not unique to serogroup B and may be expressed by other meningococcal serogroups. A detailed description of vaccine antigens and the process of vaccine development are described in the [Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration](http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php) (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).



This document updates the epidemiology of IMD in Canada; provides available vaccine efficacy, effectiveness, immunogenicity and safety information on 4CMenB vaccine, as well as reviews issues related to implementation, evaluation, surveillance and identifies evidence gaps and ongoing research needs. This guidance document contains the full recommendations of the NACI for the use of 4CMenB vaccine as well as overall program considerations.

## Methods

In June 2012, based on a proposal from the National Immunization Strategy Task Group (NIS-TG), the Communicable and Infectious Disease Steering Committee (CID-SC) approved the creation of a new, time-limited Meningococcal B Pilot Project Task Group (MBPPTG). This task group was mandated to develop guidance for use of meningococcal B vaccine by integrating scientific and technical recommendations with program and policy recommendations.

The objectives of this pilot project were to test, demonstrate, and assess a potential means to improve the process for the development of *Common Guidance* for new vaccines in Canada.

The work related to a NACI statement for the recommended use of the multicomponent meningococcal B vaccine was initiated by the Invasive Meningococcal Disease Working Group of NACI. In August 2012, this working group was transitioned to the MBPPTG for the purposes of this pilot project, which was composed of NACI representatives, Canadian Immunization Committee representatives, in addition to Canadian experts in IMD, in order to produce the final *Common Guidance* document.

A comprehensive literature search and review was completed to identify relevant evidence on the 4CMenB vaccine including safety, immunogenicity, efficacy and effectiveness of the vaccine; vaccine schedules; target populations; and other aspects of the overall immunization strategy. In addition, the burden due to IMD in Canada was reviewed. In anticipation that there would be no efficacy or effectiveness data available on the novel 4CMenB vaccine, an analogous process was taken for the NZ-OMV vaccine (MeNZB™, Novartis Vaccines, formerly Chiron), a component of 4CMenB vaccine for which effectiveness data is available. The knowledge synthesis was performed by Public Health Ontario and supervised by the MBPPTG. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence were prepared using NACI's methodological hierarchy. After a thorough review of the evidence and consultations, MBPPTG proposed provisional recommendations, pending achievement of the Notice of Compliance for market authorization in Canada. The full knowledge synthesis and review is maintained by the Public Health Agency of Canada (the Agency).

Using the analytic framework for immunization program in Canada,<sup>5</sup> the following chapters were developed and completed in December 2013, based on the provisional NACI Statement to support programmatic considerations:

- Immunization Strategies
- Social and Economic Cost and Benefits
- Program Feasibility and Acceptability
- Program Evaluation and Research
- Other Considerations
- Recommended Immunization Program

Dr. Philippe De Wals prepared the Immunization Strategies and Social and Economic Cost and Benefits chapters. Program Evaluation and Research was prepared by the Agency.

The full knowledge synthesis and literature review for the acceptability, feasibility and ethical considerations for vaccination against serogroup B meningococcus, prepared by Dr. Eve Dubé, is maintained by the Agency.

The NACI Statement, presented as Part 1, and the programmatic chapters, presented as Part 2, have been combined together and are considered the *Common Guidance* for the recommended use of the multicomponent meningococcal B (4CMenB) vaccine in Canada.

## Part 1 – National Advisory Committee on Immunization (NACI) statement for the use of 4CMenB vaccine

### Disease Characteristics and Burden

#### Disease

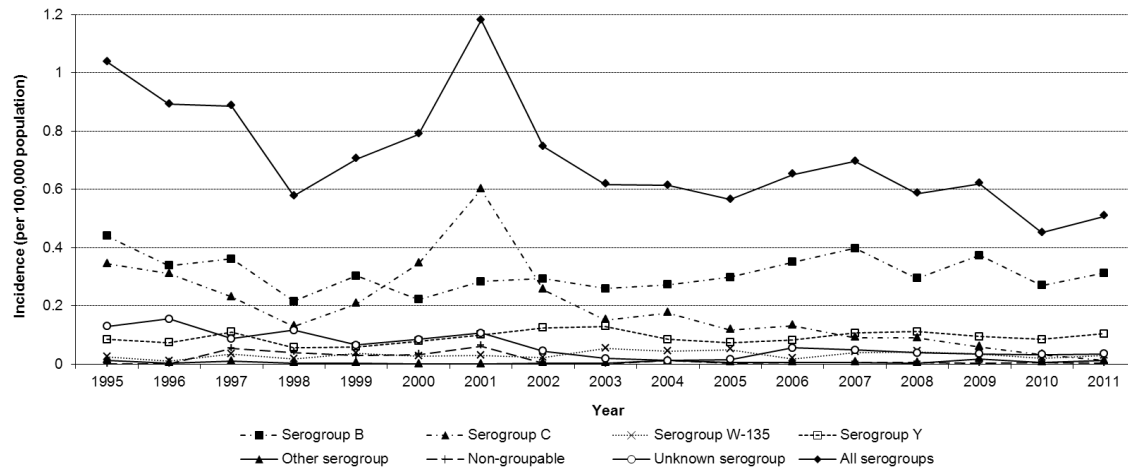
IMD is an acute and serious illness caused by the bacterium *N. meningitidis* (meningococcus). This potentially serious pathogen colonizes up to 10% of healthy individuals without causing harm. Meningococci can be classified based on the immunologic reactivity of the polysaccharide capsule into 12 different serogroups, of which five (A, B, C, W-135 and Y) are associated most frequently with IMD around the globe. Further classification into serotypes and serosubtypes can be made based on the immunologic reactivity of meningococcal outer membrane proteins (OMP). Characterization using nucleotide sequence-based methods such as genetic sequencing of *porA* and *porB* genes is used to substitute or supplement serology-based classifications.

#### Epidemiology

IMD usually presents as an acute febrile illness with rapid onset and features of meningitis or septicemia (meningococcemia), or both, and a characteristic non-blanching rash. Overall case fatality is approximately 10%, and up to a third of survivors may have long term sequelae, which can include hearing loss, neurologic disabilities, and digit or limb amputations.<sup>6,7</sup> IMD is a reportable communicable disease in all provinces and territories (P/Ts). All probable and confirmed IMD cases are reported to the P/T public health authorities Agency's Enhanced IMD Surveillance System. P/T public health and/or hospital laboratories send all meningococcal isolates to the Agency's National Microbiology Laboratory (NML) for strain characterization, including confirmation of serogroup and determination of serotype, serosubtype and sequence type/clonal complex.

Although IMD is reported year round, there is considerable variation in geographical and temporal incidence, with the majority of cases occurring between November and March. As depicted in [Figure 1](#), the overall annual incidence of IMD in Canada has ranged from 0.45 to 1.18 cases per 100,000 population from 1995 to 2011.<sup>8</sup> Between 2007 and 2011, an average of 192 cases of IMD was reported annually in Canada, with an overall average incidence of 0.57 cases per 100,000 population per year.<sup>8</sup>

**Figure 1 - Incidence of IMD (per 100,000 population) in Canada by serogroup and year, from 1995 to 2011<sup>8</sup>**



In Canada, serogroups B, C, W-135 and Y are responsible for the majority of IMD. Following the occurrence of multi-focal serogroup C outbreaks in the late 1990s and early 2000s, conjugate serogroup C vaccination programs were implemented in all Canadian P/Ts between 2002 and early 2007 ([Table 1](#)), resulting in significant decreases in serogroup C incidence in all age groups and regions.<sup>7,9-29</sup> With the declining incidence of serogroup C, serogroup B now makes up the greatest proportion of reported IMD cases in Canada (62% due to serogroup B versus 2% due to serogroup C in 2011).<sup>8</sup> From 2007 to 2011, serogroup B incidence has fluctuated slightly between 0.27 and 0.40 cases per 100,000 per year.<sup>8</sup>

**Table 1 - Summary of current meningococcal immunization programs in Canada, 2011**

Province/ Territory	Year of initial implementation of routine meningococcal C conjugate program	Current infant schedule using meningococcal C conjugate	Current adolescent schedule using meningococcal C conjugate (C) or ACYW-135 conjugate (Q)*
BC	2003	2, 12 months (since 2005)	(C) Grade 6 (since 2003)
AB	2002	2, 4, 12 months (since 2007)	(Q) Grade 9 (since 2011)
SK	2004	12 months (since 2004)	(Q) Grade 6 (since 2011)
MB	2004	12 months (since 2009)	(C) Grade 4 (since 2004)
ON	2004	12 months (since 2004)	(Q) Grade 7 (since 2009)
QC	2002	12 months (since 2002)	(C) Grade 9 (since 2013)
NL	2005	12 months (since 2005)	(Q) Grade 4 (since 2007)
NB	2004	12 months (since 2004)	(Q) Grade 9 (since 2007)
NS	2005	12 months (since 2005)	(C) Grade 7 (since 2010)
PE	2003	12 months (since 2003)	(Q) Grade 9 (since 2006)
YK	2005	2, 12 months (since 2009)	(C) Grade 6 (since 2006)
NT	2004	2, 12 months (since 2004)	(C) Grade 9 (since 2008)
NU	2007	12 months (since 2007)	(C) Grade 9 (since 2006)

*\*Only initiation dates of current adolescent meningococcal vaccine programs are provided.  
Most P/Ts initially offered meningococcal C conjugate vaccines to adolescents via either routine or  
catch-up programs between 2002 and 2005.*

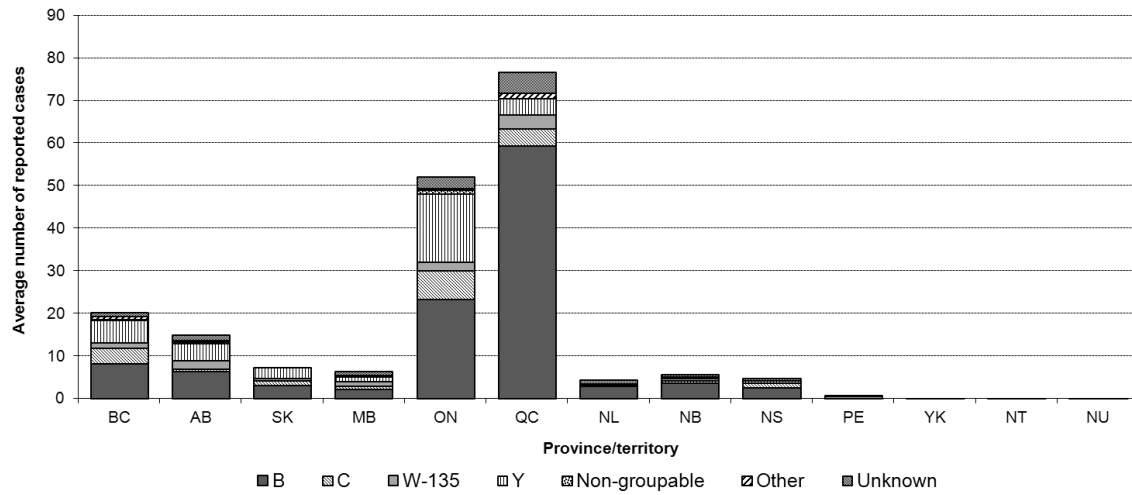
[Table 2](#) presents the number of reported cases and incidence of IMD by serogroup in 2011 as well as the mean number of cases for 2007 to 2011. It also indicates the median age and case fatality ratio (CFR) of IMD by serogroup from 2007 to 2011.

**Table 2 - Summary of the epidemiology of invasive meningococcal disease in Canada by serogroup in 2011, and between 2007-2011<sup>8</sup>**

Serogroup	2011		2007 to 2011			
	Number of cases	Incidence (cases per 100,000 population)	Average annual number of cases (range)	Average annual incidence (cases per 100,000 population)	Median age (years)	Case fatality ratio
A	0	0	0.2 (0 to 1)	0	16	0.0%
B	108	0.31	111 (92 to 131)	0.33	16	6.0%
C	4	0.01	19 (4 to 30)	0.06	44.5	15.3%
W-135	10	0.03	11.2 (7 to 14)	0.03	38	8.5%
Y	36	0.10	33.8 (29 to 37)	0.10	47	12.1%
Other	4	0.01	3 (1 to 6)	0.01	34	0%
Non-groupable	1	0	1.6 (1 to 2)	0	28	10.0%
Unknown	12	0.04	12.8 (11 to 16)	0.04	16.5	8.2%
All serogroups	175	0.51	192.4 (154 to 229)	0.57	20	8.2%

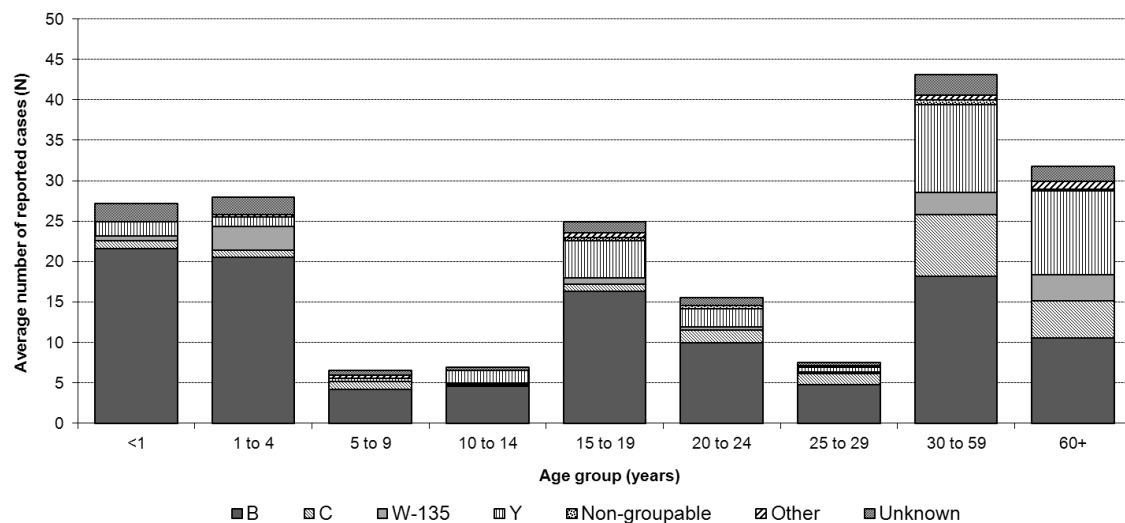
As demonstrated in [Figure 2](#), geographic differences in the serogroup distribution of IMD exist across Canada. The highest incidence of IMD and serogroup B-specific IMD occurred in Québec where, on average, 77% of cases were due to serogroup B from 2007 to 2011.<sup>8</sup> Among remaining provinces, the serogroup distribution varied, with serogroup B making up between 25% and 77% of cases on average from 2007 to 2011, depending on the region.<sup>8</sup> Very few cases were reported in the three territories and Prince Edward Island (zero to two cases per year) from 2007 to 2011, occasionally resulting in high proportions that should be interpreted with caution.<sup>8</sup>

**Figure 2 - Average reported cases of IMD in Canada by serogroup and province/territory from 2007 to 2011<sup>8</sup>**



The serogroup distribution of IMD also differs by age, with serogroup Y cases having the highest median age from 2007 to 2011 (47 years), followed by C (44.5 years) and W-135 (38 years). As seen in [Figure 3](#), the proportion of cases due to serogroup B decreases with age while conversely, the proportion of cases due to serogroups C and Y tends to increase with age.

**Figure 3 - Average reported cases of IMD in Canada by serogroup and age group in years from 2007 to 2011<sup>8</sup>**



The incidence of serogroup B is low and remains highest in infants less than one year of age with an age-specific incidence rate of 5.8 cases per 100,000 in 2011, followed by one to four year olds (1.4 cases per 100,000) and 15 to 19 year olds (0.7 cases per 100,000).<sup>8</sup> As seen in [Table 3](#), although serogroup B incidence rates follow

similar trends across P/Ts, the incidence of serogroup B among 15 to 19 year olds has been particularly high in Québec compared to other regions (2.6 cases per 100,000 in 2011).<sup>8</sup>

**Table 3 – Average annual incidence (per 100,000 population) of IMD serogroup B in Canada by age group in years, and province/territory from 2007-2011<sup>8</sup>**

P/T	Less than 1	1 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 59	60 and greater	All ages
BC	5.02	0.35	0.18	0	0.21	0.33	0.13	0.10	0.09	0.18
AB	3.61	0.65	0.10	0.09	0.08	0.28	0.06	0.10	0	0.17
SK	10.37	1.19	0.94	0	0	0	0	0.05	0.10	0.29
MB	0	1.34	0	0	0.22	0.22	0.48	0.08	0	0.16
ON	3.02	0.78	0.06	0.10	0.23	0.29	0.09	0.10	0.10	0.18
QC	11.95	3.05	0.57	0.71	2.57	1.01	0.53	0.20	0.36	0.76
NL	16.38	6.28	0	0	0.60	0	0.70	0.09	0.17	0.55
NB	5.38	4.16	0.53	0.50	0.42	0.43	0	0.24	0.24	0.48
NS	2.30	0.58	0.42	0.76	0.34	0.30	0	0.15	0.19	0.26
PE	0	0	0	0	0	0	0	0	0.65	0.14
YK	0	0	0	0	0	0	0	0	0	0
NT	0	7.51	0	0	0	0	0	0	0	0.45
NU	24.66	0	0	0	0	0	0	0	0	0.60
Canada	5.78	1.40	0.23	0.23	0.73	0.43	0.21	0.12	0.16	0.33

Between 2007 and 2011, an average of 111 cases of serogroup B IMD were reported annually in Canada. As seen in [Table 4](#), during this time period the largest number of cases was reported in the province of Québec and in children less than 5 years of age.<sup>8</sup>

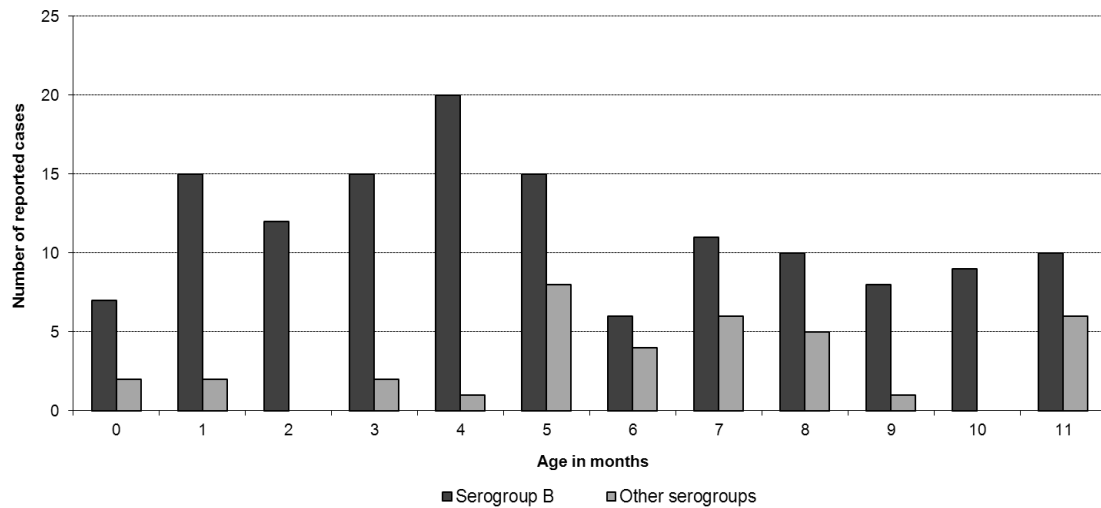


**Table 4 – Average annual number of reported of IMD serogroup B cases in Canada by age group in years and province/territory, 2007-2011<sup>8</sup>**

P/T	Less than 1	1 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 59	60 and greater	All ages
BC	2.2	0.6	0.4	0	0.6	1	0.4	2	0.8	8
AB	1.8	1.2	0.2	0.2	0.2	0.8	0.2	1.6	0	6.2
SK	1.4	0.6	0.6	0	0	0	0	0.2	0.2	3
MB	0	0.8	0	0	0.2	0.2	0.4	0.4	0	2
ON	4.2	4.4	0.4	0.8	2	2.6	0.8	5.6	2.4	23.2
QC	10.4	10.2	2.2	3	12.8	5	2.8	6.8	6	59.2
NL	0.8	1.2	0	0	0.2	0	0.2	0.2	0.2	2.8
NB	0.4	1	0.2	0	0.2	0.2	0	0.8	0.4	3.6
NS	0.2	0.2	0.2	0.4	0.2	0	0	0.6	0.4	2.4
PE	0	0	0	0	0	0	0	0	0.2	0.2
YK	0	0	0	0	0	0	0	0	0	0
NT	0	0	0	0	0	0	0	0	0	0.2
NU	0	0	0	0	0	0	0	0	0	0.2
Canada	21.6	20.6	4.2	4.6	16.4	10	4.8	18.2	10.6	111

As depicted in [Figure 4](#), from 2005 to 2011, 61% of IMD serogroup B cases in infants under one year of age occurred within the first six month of life.<sup>8</sup>

**Figure 4 - Age distribution of reported invasive meningococcal disease cases among infants less than one year of age in Canada from 2005 to 2011 by serogroup and age in months<sup>8</sup>**



#### ***Antigenic and Genetic Characterization of Serogroup B IMD by Current Routine Methods***

From 2007 to 2011, among cases known to be confirmed by culture or PCR, 85% of cases were confirmed by culture, 10% were confirmed by PCR, and 5% were confirmed by both (method of confirmation not stated for 3% of the cases). MenB isolates in Canada are characterized by serotyping and serosubtyping using monoclonal antibodies;<sup>30</sup> PorA genotype determination;<sup>31,32</sup> and Multilocus Sequence Typing (MLST) classification into sequence type (ST) and clonal complex (cc) according to methods described in the [Neisseria.org](http://neisseria.org) website (<http://neisseria.org/>).

Analysis of serogroup B isolates from 2001 to 2011 has revealed extensive heterogeneity in the antigenic and genetic characteristics of circulating strains across the country, with the exception of Québec and New Brunswick.<sup>33,34</sup> In the province of New Brunswick, an increase in IMD in 2008 to 2011 was due to an ST-154 clone of MenB characterized as B:4:P1.4, PorA genotype P1.7-2,4,37 (member of the ST-41/44 cc). Outside of New Brunswick, this clone has been uncommon, e.g. accounting for only 5% of all invasive MenB isolates in Ontario between 2001-2010.<sup>33</sup> In Québec, the majority (76%) of the serogroup B isolates belonged to a highly homogeneous strain in the ST-269 cc with 92% being ST-269 and 86% expressing the PorA genotype of P1.19-1, 15-11, 36.<sup>24,34</sup> In contrast, in Ontario, of the 20 case isolates that belong to the ST-269 cc collected between 2001 and 2010, seven different sequence types and 11 different PorA genotypes were identified.<sup>33</sup>

Relative to the porin A (PorA) type P1.4 antigen contained in the 4CMenB vaccine, among serogroup B cases from 2007 to 2011, 8.5% were due to strains expressing this antigen. There were differences seen across P/Ts, with P1.4 most commonly reported in the Maritimes (33% to 83% of cases depending on the province), but

rarely in other provinces such as Québec (1%) and not at all reported in Manitoba and the Territories. Differences also occurred across age groups, with P1.4 most commonly reported in children aged one to four years of age (14% of serogroup B cases) and least commonly reported in adolescents aged 15 to 19 years (4% of serogroup B cases).

### *Serogroup B IMD Outcomes*

From 2007 to 2011, 8.2% of nationally reported IMD cases died. Case fatality ratios (CFR) differed by serogroup, with serogroup C having the highest CFR at 15.3% and B having the lowest at 6.0% ([Table 2](#)).

There are a few studies that specifically review outcomes of serogroup B disease. A study conducted by the Immunization Monitoring Program Active (IMPACT) reported outcomes of 413 laboratory confirmed Canadian serogroup B cases that were hospitalized between 2002 and 2011.<sup>6</sup> The mean length of hospital stay in this study was 11.2 days and 60.5% of cases required care in the intensive care unit. Among cases admitted to the ICU, 45% required assisted ventilation and 36% required blood pressure support using inotropes. Of 391 survivors, 19% had at least one sequelae due to their infection at or shortly after discharge, with 23% requiring inpatient rehabilitation. Most commonly reported sequelae included deafness (7.2%), skin scarring (6.4%), amputation (3.8%), neurologic sequelae (3.6%), seizures (2.6%), and renal dysfunction (2.0%). Long term outcomes were not reported in this study. However, a case-control study of 245 serogroup B meningococcal disease survivors in the UK, reported major disabling deficits in one tenth, and one or more deficits in physical, cognitive, and psychological functioning, with the additional burden of memory deficits and executive function problems in approximately a third of survivors.<sup>6,9</sup>

### *International Burden*

Like Canada, IMD is endemic in many countries around the world with regional differences in the serogroup distribution.<sup>35</sup> In Europe, Australia, and New Zealand, the most commonly reported serogroup is B, followed by C, although recent increases in Y have been reported in some areas of Europe.<sup>35</sup> In the United States, serogroups B and C are most commonly reported, followed closely by Y. There is variation in the serogroup distribution across South America, and although serogroup B followed by C is predominant in many countries, W-135 and Y make up a large proportion in others.<sup>35</sup> Little is known about endemic epidemiology in Asia.<sup>35</sup> Africa's most affected region, an area of sub-Saharan Africa known as the "meningitis belt" that stretches from Senegal to Ethiopia, is affected by large serogroup A outbreaks each year, although W-135 has also been predominant in recent years.<sup>35,36,37</sup> In 2011, several countries belonging to the "meningitis belt" reported historically low incidence rates of confirmed IMD cases following the introduction of national serogroup A conjugate vaccine programs.<sup>35,38</sup>

In the last few decades, serogroup B outbreaks have been reported in regions around the world including the United States (Oregon), New Zealand, Norway, Chile, Cuba, France, Uruguay, Spain, Japan and Brazil, among others.<sup>16,35,39–43</sup> In response to specific outbreaks, several tailor-made, outer membrane vesicle (OMV) serogroup B vaccines have been produced and used in various serogroup B outbreaks with good effectiveness, including VA-MENGOC-BC® in Cuba during the 1980s and Uruguay in 2001, MenBvac® in Norway during the 1970s and 1980s and France from 2006 to 2009, and MenNZB™ in New Zealand from 2004 to 2008. Due to the nature of IMD epidemiology, associated mortality and morbidity, the World Health Organization has advised on the use of enhanced IMD surveillance for timely and appropriate prevention and management of IMD outbreaks and emerging *N. meningitidis* strains.<sup>35,43</sup>

## Vaccine Characteristics

### *Preparations Authorized for Use in Canada*

While the polysaccharide capsule provided the basis for previously approved meningococcal vaccines against serogroups A, C, W-135 and Y, the serogroup B capsular polysaccharide has significant similarity to the human neural cell adhesion molecule (nCAM) and cannot be used for vaccine development, primarily due to concerns about creating auto-antibodies. For this reason efforts to develop a serogroup B vaccine have focused on OMVs and other surface exposed protein antigens. Single component serogroup B OMV vaccines have been used in meningococcal serogroup B outbreak settings and appear to be safe and effective.<sup>44–48</sup>

The multicomponent meningococcal vaccine (4CMenB) Bexsero® (Novartis Vaccines), authorized for use on December 6, 2013, is the first serogroup B-specific vaccine available in Canada. The vaccine contains 25 µg of detoxified OMV containing PorA P1.4 from the New Zealand MenNZB™ vaccine, plus three purified *N. meningitidis* serogroup B protein antigens identified by reverse vaccinology: 50 µg of factor H binding protein (fHbp, sub-variant 1.1) fused to genome-derived neisserial antigen 2091 (GNA2091), 50 µg of Neisseria heparin binding antigen (NHBA peptide 2) fused to genome-derived neisserial antigen 1030 (GNA1030), and 50 µg of single Neisserial adhesion A (NadA, subvariant 3.1).<sup>29,49</sup> Antigens contained in the vaccine are adsorbed on 1.5 mg of aluminum hydroxide which corresponds to 0.5 mg of elemental aluminum per vaccine dose. 4CMenB vaccine has been authorized for use in persons from 2 months through 17 years of age. A detailed review of all vaccine 4CMenB vaccine components can be found in the Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).

### *Efficacy and Effectiveness*

The conducted literature search did not identify any published studies on the efficacy or effectiveness of the 4CMenB vaccine. It should be noted that in non-epidemic settings pre-licensure efficacy studies for meningococcal vaccines are not considered feasible due to significant challenges in conducting such studies (i.e. relative rarity of endemic IMD), and other conjugate meningococcal vaccines have been licensed based on immunogenicity.

NZ-OMV monovalent vaccine effectiveness has been estimated between 33–84%, depending on the age cohort, number of doses, modeling methods and time from vaccination (i.e. waning immunity). No studies explicitly describe herd effects of the NZ-OMV monovalent vaccine, but in a declining outbreak setting a drop in IMD rates has been observed with its introduction. It is not known if the decrease in serogroup B IMD in New Zealand was due to secular trends, the immunization program, both, or any other factors.<sup>43–45,50–52</sup> It is not clear yet whether the NZ-OMV component in combination with the other antigens in 4CMenB will have the same protective effectiveness as the monovalent vaccine. At the same time, findings from phase II trials comparing the immunogenicity of 4CMenB vaccine to the candidate vaccine without NZ-OMV suggest that, in addition to inducing specific antibodies to the P1.4 PorA antigen, the NZ-OMV component may have an adjuvant effect on the immunogenicity of other 4CMenB vaccine components.<sup>49,53,54</sup>

### *Herd Immunity*

Since 4CMenB vaccine has not yet been used at a population level, it is not known if it will confer herd immunity. Preliminary data obtained from an oral presentation submitted for the 31st Annual Meeting of the European Society for Pediatric Infectious Disease indicate, in the primary analysis, no reduction in nasopharyngeal carriage following immunization of 932 university students with two doses of 4CMenB vaccine. Other vaccines that eliminate carriage including serogroup C meningococcal conjugate vaccine, have conferred herd immunity. For example, in a comparison of one year (July 1998-June 1999) prior to the introduction of serogroup C meningococcal conjugate vaccine to the routine childhood immunization schedule in the UK to a one year (July 2001-June 2002) period after the program began, a 35% (95% CI: 20%, 49%) decrease in the incidence of serogroup C IMD was observed among adults greater than 25 years old. In this vaccine ineligible group, the rate of serogroup C IMD went from 0.53/100 000 to 0.34/100 000.<sup>54</sup> Ongoing unpublished studies examining the effect of 4CMenB vaccine on nasopharyngeal carriage of meningococci are expected to provide additional information about its potential to affect herd immunity and to confer population-level benefits.

### *Immunogenicity*

Immunogenicity outcomes most commonly used and approved by regulators to determine susceptibility and short-term immunity to IMD are human complement serum bactericidal activity (hSBA) levels and enzyme linked immunosorbent assays

(ELISA). In previously conducted trials of OMV vaccines, the proportions of vaccines with  $\geq 4$ -fold rises in hSBA pre- to post-vaccination or hSBA titres of  $\geq 1:4$  have been correlated with clinical efficacy.<sup>55</sup>

Immunogenicity of 4CMenB vaccine was measured and reported in ten trials including approximately 5800 healthy participants, of whom 4000 were children aged 2 to 24 months, 84 were children 40-43 months and 1738 were adolescents or adults aged 11 to 55 years. These trials assessed the post-vaccination immune response to each vaccine antigen independently, using a combination of hSBA titres (of  $\geq 1:4$  or  $\geq 1:5$ ) against selected reference strains H44/76 (fHbp Novartis sub-variant 1.1), 5/99 (NadA sub-variant 2.2) and NZ98/254 (PorA P1.7-2,4). Studies that were conducted prior to the identification of a reference strain that primarily expresses NHBA vaccine antigen peptide 10 (M10713) measured the quantity of antigen-specific IgG. Only one publication by Vesikari et al (2013) reported the percentage of participants with hSBA titres against reference strain M10713 in infants aged  $\leq 12$  months.<sup>56,57,76</sup>

In infants aged  $\leq 12$  months, 4CMenB vaccine was found to be immunogenic after at least two doses and an anamnestic response to a booster dose, given at 12 months of age, was also evident. The infant vaccination schedules assessed include: three doses given at 2, 3 and 4 months of age; three doses given at 2, 4 and 6 months of age with or without a booster at 12 months of age; and three doses given at 6 to 8 months of age, 60 days later and 12 months of age. In the group that received a booster dose at 12 months of age, hSBA titres waned prior to the booster dose, with only between 34% and 89% of infants meeting the antibody threshold, depending on the antigen.<sup>49</sup> Further, 12 months after the booster dose, at age 24 months, hSBA titres were low, especially against strain NZ98/254.<sup>58</sup> Non-inferiority was also demonstrated when the 4CMenB was administered with concomitant vaccines (Infanrix-hexa<sup>®</sup> and Prevenar<sup>®</sup>) compared to when it was administered alone; the exception was strain NZ98/254 where a higher proportion of infants obtained hSBA titres  $\geq 1:5$  when these vaccines were given on separate occasions, suggesting that the NZ-OMV component may be impacted by schedule.<sup>59</sup> In a different trial, similar proportions of infants reached the hSBA threshold after a booster dose, with or without concomitant Priorix-Tetra<sup>™</sup>.<sup>57,76</sup>

In children aged 12 to 24 months, 4CMenB vaccine was found to be immunogenic against strains H44/76, 5/99 and NZ98/254 after two doses (given at either 12 and 14 or 13 and 15 months of age),<sup>60</sup> but not after a single dose given at 12 months of age.<sup>49</sup> Geometric mean titres (GMTs) were between 32 and 627 one month after the second dose of 4CMenB vaccine, compared to between 1.0 and 1.2 at baseline. However, hSBA titres waned after 9 to 10 months (when measured at age 24 months) and were lowest against strain NZ98/254.<sup>58</sup> A third dose of 4CMenB vaccine given at 24 months of age stimulated hSBA titres of  $\geq 1:5$  against strains H44/76, 5/99 and NZ98/254 in all participants.



For the 84 children who received two doses of 4CMenB vaccine at 40 and 42 months of life, seroprotection was achieved one month after the second dose for each of the reference strains by 70-100% of participants, depending on reference strain. The proportion with seroprotective titres was lowest against strain M10713, which measures response to the NHBA antigen.<sup>61-64</sup>

In adolescents and adults, 4CMenB vaccine was found to be immunogenic against strains H44/76, 5/99 and NZ98/254 after at least one dose, although higher GMTs were seen after two compared to one dose of the vaccine; at 6 months, at least 91% of adolescents had hSBA titres of  $\geq 1:4$  for each of the three reference strains after two or three doses, compared to 73-76% after one dose.<sup>65</sup> In adults, four months after the second dose, 96% and 100% had hSBA titres of  $\geq 1:4$  against strains H44/76 and 5/99, respectively, compared to 67% against strain NZ98/254.<sup>66</sup>

Overall, compared to the other selected reference strains, immune responses were generally lowest to strain NZ98/254, which expresses multiple antigens found in the 4CMenB vaccine including identical PorA (P1.4) and NHBA (peptide 2), as well as the cross-reactive fHbp variant 1.<sup>67</sup> It has been suggested that the low response of vaccinated sera with this strain may be attributable in part to the low level of expression of these antigens by NZ98/254.<sup>49</sup>

Findings from phase II trials comparing the immunogenicity of 4CMenB vaccine to that of a candidate recombinant meningococcal B (rMenB) vaccine without the OMV component, suggest an adjuvant effect of the OMV component.<sup>49,53</sup> Studies of the immunogenicity of NZ-OMV vaccine among infants and children in New Zealand showed a beneficial effect of a third dose.<sup>68</sup> However, similar to 4CMenB vaccine, a fairly rapid decline of bactericidal antibodies was seen after three doses.<sup>69</sup> A fourth dose of NZ-OMV given at 10 months of age (5 months after the third dose) elicited a booster response, increasing the percentage of infants achieving the hSBA threshold from 48% after dose three to 69% after dose four.<sup>69</sup> Post-licensure NZ-OMV studies estimated the vaccine effectiveness to be between 53.3% and 84%.

The longest period in which studies to date have measured immunogenicity of 4CMenB vaccine was at 40 months of age, 28 months after the completion of 3+1 infant schedule.<sup>58</sup> In toddlers immunogenicity was measured 12 months after the last dose of a 2-dose series,<sup>58</sup> in adolescents 24 months after the last dose of a one-, two-, or three-dose schedule,<sup>65</sup> and in adults one month after the third dose.<sup>66</sup> Preliminary evidence indicates waning immunity to the PorA antigen. Because outside these short periods there are no data regarding circulating antibody levels, the duration of protection will need to be addressed in future studies, particularly as it appears that high titres of circulating anti-meningococcal antibodies are required to prevent disease after exposure.<sup>70</sup>

A detailed review of 4CMenB vaccine immunogenicity can be found in the Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).

### ***Meningococcal Antigen Typing System (MATS)***

The MATS assay developed by Novartis uses antigen-specific ELISA to measure the immunologic cross-reactivity and quantity of NHBA, NadA and fHbp antigens in a meningococcal isolate to predict the level of vaccine protection against a specific strain. In addition to the MATS assay, PorA genotyping information from the tested meningococcal strains is used for predicting the immune response. MATS is an *in vitro* prediction of how well 4CMenB vaccine will protect against currently circulating serogroup B meningococcal strains. At the time of the literature review, this prediction is based on the correlation of MATS and hSBA that was reported in only one published study.<sup>71,72</sup> Using pooled sera from 13-month-olds who had received 4CMenB (3+1) schedule, 89% of tested strains that were above the positive bactericidal threshold for one or more antigens were “killed” by the hSBA. Seventy-seven percent of tested strains that were below the positive bacterial threshold were also “not killed” by the hSBA. This means that 11% were falsely positive on MATS (predicted to have been killed but were not) and 23% were falsely negative (predicted to not be killed but were). Possible reasons for the potential underestimation of effectiveness include immunogenicity against other antigens present in OMV that are not captured in MATS, lack of assay ability to capture the synergistic action of antibodies to different antigens and the repression of NadA expression *in vitro*. Potential reasons for the overestimation of effectiveness include over-expression of target antigens *in vitro*.

IMPACT investigators have looked for presence of vaccine antigen surface proteins on IMPACT derived Canadian strains using the MATS assay.<sup>73,74</sup> Susceptibility was assessed for 157 serogroup B meningococcal strains obtained in 12 Canadian cities through population-based catchment-area surveillance of over 17 million adults and children (just over 50% of the Canadian population) from 2006-2009. Overall, the 4CMenB vaccine MATS predicted strain coverage in Canada was 66% (95% CI: 46%, 78%), with 26% of strains covered by one, 29% covered by two and 11% covered by three vaccine antigens. Coverage by antigen was as follows: NHBA 51% (95% CI: 21%, 71%), NadA 1% (95% CI: 0.6%, 3%), fHBP 52% (95% CI: 40%, 59%), and PorA 13% (95% CI: 8%, 18%). Of the 6 isolates from fatal cases, 4 (67%) were predicted covered, as were 23 of the 34 (68%) isolates from cases that resulted in long term sequelae. The authors considered 4CMenB vaccine to protect against a strain if the strain possessed PorA P1.4 or had a relative potency above the positive bactericidal threshold for fHbp, NHBA or NadA. For isolates from children <1 year old, 49% (95% CI: 29%, 71%) were covered by the vaccine, whereas 74% (95% CI: 61%, 90%) of isolates from those aged 1-4 years and 81% (95% CI: 59%, 84%) from those aged 5-19 years were covered. Sixty five percent (95% CI: 39%, 72%) of isolates from adults aged 20 years and older were covered by the vaccine. By province, the predicted coverage of 4CMenB ranged from 43% to 100% and



reflected the strains circulating within each region and the level of antigen expression within each isolate. A very large proportion (95%) of the 37 ST-269 isolates matched the vaccine. ST-269 was the most frequent clonal complex in Québec.<sup>74,75</sup>

### **Adverse Events**

Across nine 4CMenB vaccine trials reporting safety, outcomes were measured in approximately 4,800 infants less than 12 months of age, 1600 children aged 12 to 24 months, 84 children 40-43 months of age and 1738 adolescents or adults aged 11 to 55 years. In these trials, solicited local and systemic reactions were recorded during a seven-day period following vaccination and serious and other adverse events were reported up to six months after the last dose of 4CMenB vaccine. The literature search did not identify any studies of the safety and reactogenicity of 4CMenB vaccine in children ages 4 to 10 or adults over the age of 55 years.

Among infants and children up to 12 months of age, most commonly reported local and systemic adverse events following vaccination with 4CMenB vaccine included erythema, induration, fever and sleepiness or irritability. Among infants, similar proportions of local reactions at the 4CMenB injection site were observed when 4CMenB vaccine and routine infant vaccines were given on separate occasions versus together, except for pain which was higher following concomitant administration.<sup>59</sup> Higher proportions of infants with solicited systemic reactions, including fever, were observed when 4CMenB vaccine was given together with Infanrix-hexa® and Prevenar®. When given concomitantly, temperature  $\geq 38^{\circ}\text{C}$  was reported in up to 61% children, compared to 38% when the 4CMenB vaccine was given alone and 33% when only routine vaccines were given. The fever was more common after the first or second dose of 4CMenB vaccine than the third dose and occurred mostly within the first six hours after vaccine administration, with very few fevers persisting beyond 2 days following vaccination.<sup>59,76,77</sup> In the only infant study that used Pediacel® as the DTaP-IPV-Hib vaccine, the proportion that experienced fever following concomitant administration with 4CMenB vaccine was comparatively lower (9.2% all doses, 18% after the first dose). However, this study only included 46 4CMenB vaccine recipients and is too small to allow any conclusions to be drawn regarding the impact of differences in formulation of routine infant vaccines on fever after simultaneous administration of 4CMenB vaccine.<sup>49</sup>

Among children 12-24 months old, the solicited local and systemic reactions were common and included tenderness, induration, fever, sleepiness or irritability. Systemic reactions were generally higher among children that received 4CMenB vaccine with Priorix-Tetra™. A higher proportion of children experienced temperatures of  $\geq 38^{\circ}\text{C}$  when 4CMenB vaccine was given concomitantly with Priorix-Tetra™, primarily due to two risk periods for fever occurring at 1-4 days (4CMenB vaccine) and 5-28 days (Priorix-Tetra™). In children who had previously received

the 4CMenB vaccine at 2, 4 and 6 months of age, a booster dose of 4CMenB increased the reported rate of fever when given concomitantly with Priorix-Tetra™ (48%) compared to when given separately (40%).<sup>57,60,76</sup>

The 4CMenB vaccine was provided to only 84 children aged 40 to 42 months. In these children, up to 18% experienced fever and 7 participants experienced severe transient arthralgia, 2 of whom reported arthralgia after both first and second vaccination. Local reactions were very common in this group and included pain (up to 92%), erythema (up to 98%), induration (up to 50%) and swelling (up to 70%).<sup>61,78</sup>

Among adolescents, proportions of local reactions after 4CMenB vaccine were somewhat similar after each dose, with a slight decrease in percentages after the second and third dose compared to after the first dose. Solicited local reactions were reported from 39% (swelling) up to 86% (pain) of 4CMenB vaccine recipients, while systemic reactions were reported in 4% (fever  $\geq 38^{\circ}\text{C}$ ) up to 51% (malaise) of 4CMenB vaccine doses (all doses combined).<sup>65</sup> Fever was significantly higher following 4CMenB vaccine compared to an alum-containing control (4% vs. 2%,  $p < 0.01$ ), as was the proportion of 4CMenB vaccine recipients that reported using antipyretic drugs (4% vs. 2%,  $p < 0.02$ ). In two adult studies, solicited local reactions were reported by 47% (erythema) up to 98% (pain) of 4CMenB vaccine recipients, while solicited systemic reactions were reported by 2.6% (fever) up to 38.1% (malaise) (all doses combined). Twelve percent of adolescents and 9% of adults reported staying home as a result of 4CMenB vaccination.

According to the authors, no increase in febrile seizures was seen in the initial reports from trials of 4CMenB vaccine.<sup>79–81</sup> Based on the Vesikari et al (2013) study, 4 seizures (all of which were accompanied by fever but two of which were reported as febrile seizures) occurred among 2478 infants < 12 months old within 24 hours of receipt of 4CMenB vaccine and routine vaccines.<sup>76</sup> In a group of 84 children given a two-dose primary series of 4CMenB vaccine at 40 and 42 months of age, only one febrile seizure was reported eight hours after the receipt of a second dose.<sup>61,63,78</sup>

In addition, a total of 7 cases of suspected Kawasaki Disease (KD) were reported in phase 2 and phase 3 clinical studies (6 cases were reported in vaccine recipients and one in a control subject). This is a relatively high number when compared to the very low background incidence of KD. No definitive causal relationship has been determined by the study's authors.<sup>76</sup>

### **Aluminum-Containing Placebo**

In the only placebo-controlled trial of 4CMenB vaccine, by Santolaya *et al* (2012), there was comparable reactogenicity between 4CMenB vaccine and an aluminum hydroxide control.<sup>65</sup> Rather than an inert, non-reactive placebo, the authors used a placebo containing aluminium, an adjuvant, as their control since 4CMenB vaccine also contains 1.5 mg of aluminium hydroxide. When interpreting the safety data

from this trial, potential inflation of the adverse events profile of the reactogenic placebo and the consequent artificial increase of the study vaccine's safety profile should be taken into consideration.

A detailed review of studies concerning 4CMenB related vaccine safety can be found in the Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).

#### ***Vaccine Administration and Schedule***

4CMenB vaccine is supplied in packs of one or ten 0.5 mL pre-filled syringes with or without needles. The tip cap of the syringe may contain natural rubber latex. There is no reconstitution or dilution required prior to administration. It must be shaken before use to ensure a homogenous suspension. 4CMenB vaccine should be administered through intramuscular injection into the deltoid or anterolateral thigh, depending on the age of recipient.

Vaccine schedule varies with age at administration. The manufacturer suggests for infants who begin primary 4CMenB immunization between the ages of 2 months and 5 months, that three doses should be given, with an interval of at least one month between doses. This series is to be followed by a fourth dose (booster dose) administered between 12 and 23 months of age. The manufacturer advises a three dose schedule for infants who begin the series between ages 6 and 11 months. The first two doses should be separated by an interval of two months (rather than one month as used in the accelerated option for younger infants) and a third dose is recommended between 12 and 23 months of age, no less than two months after the second dose.

When primary immunization is initiated in children aged 12 months to 10 years, the manufacturer suggests two 2 doses of 4CMenB vaccine separated by a two month interval.

For persons aged 11 through 17 years of age, the manufacturer recommends two doses given at least one month apart.

Although the manufacturer currently does not provide an adult schedule, in clinical trials of individuals from 18 to 55 years of age, two doses given at least one month apart have shown to be immunogenic and safe. The duration of protection after primary immunization with 4CMenB vaccine is unknown. Therefore, the need for a booster dose, after any of the recommended immunization schedules is yet to be determined.

#### ***Storage Requirements***

4CMenB vaccine should be stored in the original package, to protect the vaccine from light, in a refrigerator at +2 to +8°C and should not be frozen.

### *Simultaneous Administration with Other Vaccines*

4CMenB vaccine has been given simultaneously with a hexavalent tetanus-diphtheria containing infant vaccine, heptavalent pneumococcal conjugate vaccine (PCV7), serogroup C meningococcal vaccine and MMRV. The only study that compared simultaneous administration of 4CMenB vaccine with other vaccines to separate administration schedules was a multicenter phase IIB trial conducted at 60 sites in six European countries and involving 1571 infants. In this study, titres to some of the 4CMenB vaccine test strains were lower when the vaccine was given simultaneously with Prevenar® and Infanrix-hexa® but statistical non-inferiority criteria were met for all but the comparison of the separate schedule versus concomitant 2, 4, 6 month schedule against strain NZ98/254, suggesting that concomitant administration with DTaP-IPV-Hib-HepB and PCV7 does not significantly alter the immunogenicity of 4CMenB vaccine.<sup>59</sup> However, as described in the safety section, higher rates of fever were observed with simultaneous administration of 4CMenB vaccine and routine infant vaccines (DTaP-IPV-Hib-HepB and PCV7) versus when they were separated. This observation needs to be considered in the Canadian context as some jurisdictions use all of these vaccines as a part of their current publicly funded programs.

Regarding the effect of 4CMenB vaccine on the immunogenicity of other vaccines, in the Gossger et al (2010) trial comparing the immunogenicity of three different 4CMenB vaccination schedules, pre-specified non-inferiority criteria of routine vaccine responses when Infanrix-hexa® and Prevenar® were given concomitantly with 4CMenB vaccine at 2, 3 and 4 months of age to routine vaccines alone was met for all routine vaccine antigens with the exception of pertussis' pertactin and pneumococcal serotype 6B.<sup>59</sup> The clinical significance of this finding is unknown.

In the Vesikari et al (2010) trial comparing different 4CMenB vaccine lots given with concomitant Infanrix-hexa® and Prevenar®, at 2, 4 and 6 months of age, pre-specified non-inferiority criteria of routine vaccination responses were met for all vaccine antigens, with the exception of polio 2 when 4CMenB vaccine was given concomitantly with Infanrix-hexa® and Prevenar® compared to Infanrix-hexa® and Prevenar® given alone.<sup>56,76</sup>

In the Vesikari et al (2011) extension study, nearly all participants (97–100%) had immune responses to the four components of Priorix-Tetra™; responses were not significantly different when Priorix-Tetra™ was given with or without 4CMenB vaccine.<sup>57,76</sup>

A detailed review of evidence concerning concomitant use of 4CMenB with other vaccines can be found in the [Literature review on serogroup B invasive meningococcal disease: epidemiology, multicomponent meningococcal B vaccine characteristics and other factors for consideration](http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php) (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).

### **Contraindications and Precautions**

4CMenB vaccine is contraindicated in persons with a serious allergy to any vaccine component or previous dose. There are no studies of 4CMenB vaccine in pregnant or lactating women or in persons less than two months and over 55 years of age.

Immunogenicity and safety studies to date have excluded persons with chronic medical conditions, including those with increased risk of IMD such as terminal complement deficiencies. As such, it is unknown if there are any contraindications to or precautions for the use of 4CMenB vaccine in these groups.

Some 4CMenB vaccine studies excluded persons with history of previous serogroup B IMD and others excluded persons with any IMD in the past, regardless of serogroup.<sup>49,53,59</sup> Thus, it is unknown if there are any contraindications to or precautions for the use of 4CMenB vaccine in those with previous meningococcal infection.

### **Other Considerations**

#### ***Implications of Acetaminophen***

Prymula et al (2011) assessed the impact of prophylactic acetaminophen on the immunogenicity and safety of routine vaccines (Infanrix-hexa® and Prevenar®) when given concomitantly with 4CMenB vaccine at 2, 3 and 4 months of age.<sup>82</sup> There were no significant differences in the immunogenicity of 4CMenB vaccine against reference strains H44/76-SL, 5/99 and NZ98/254 when co-administered with routine vaccines with or without prophylactic acetaminophen. It is not clear whether parental administration of acetaminophen, independent of the study, was included in usual care in the non- acetaminophen group, or if this group was instructed not to take acetaminophen. Prophylactic acetaminophen was found to reduce febrile events after vaccinations. The proportion of infants with temperature  $\geq 38.5^{\circ}\text{C}$  was nearly 50% lower in infants who received acetaminophen than those who did not (51% vs. 25%). Although temperature  $\geq 39.5^{\circ}\text{C}$  was uncommon in both groups, a smaller proportion of infants had fever ( $\geq 39.5^{\circ}\text{C}$ ) when given acetaminophen (1% vs. 5%). Additionally, the proportion of infants with fever ( $\geq 38.5^{\circ}\text{C}$  and  $\geq 39.5^{\circ}\text{C}$ ) decreased with each successive dose of 4CMenB vaccine. The immunogenicity of the 4CMenB vaccine was not affected by the use of acetaminophen.

Interestingly, when parents of the open-label subset were informed of potential fever events after vaccination in an on-going phase III study<sup>76</sup>, the probability of medically attended fever among infants who received 4CMenB vaccine concomitantly with routine vaccines (Infanrix-hexa® and Prevenar®) was lower in the open-label subset than the observer-blind subset where parents were not informed of the potential for fever (1.42% vs. 5.27%). Although 93% of the parents had reported using analgesics or antipyretics after one of the 2,4, or 6-month doses, details on whether they were counseled to prophylactically administer medication remains unclear.

The results of Prymula et al (2011) imply that routine prophylactic administration of acetaminophen may be an appropriate strategy to counter high rates of fever among infants vaccinated with 4CMenB vaccine.<sup>82</sup> A practice such as this would stray from current practice. Although there are no recommendations in the Canadian Immunization Guide regarding prophylactic use of antipyretics at the time of immunization, parental administration of antipyretic drugs, such as acetaminophen or ibuprofen, is generally recommended by health care providers for treatment of the self-limited fever that occurs after vaccination. There is not a typical practice among health care providers regarding prophylactic administration of antipyretics to *prevent* vaccine-related fever; some may recommend to do so and others may not. As well, there are no safety data on a practice whereby antipyretics are routinely given accompanying each dose of a given vaccine, as the Prymula et al. study seems to suggest.<sup>82</sup>

#### ***Cross-reactivity with Other Meningococcal Serogroups***

Sub-capsular proteins found in 4CMenB vaccine may be expressed in all meningococcal serogroups and there are data to indicate that 4CMenB could potentially confer protection against other IMD causing strains.<sup>83–85</sup> Prevalence and genetic diversity of 4CMenB vaccine containing antigens in strains beyond serogroup B will need to be further investigated in Canada in order to determine their susceptibility and potential impact on existing vaccination programs.



## Part 2 – Analytic Framework for an 4CMenB immunization program

### Immunization Strategies

#### Purpose and Objectives of a 4CMenB Immunization Program

In order to achieve consensus on the goals of immunization programs implemented in Canada's P/Ts, a national conference on vaccine-preventable diseases was organized in 2005 as part of the National Immunization Strategy.<sup>87</sup> The goal was to reduce illness and death due to serogroup C invasive meningococcal (*Neisseria meningitidis*) infections. At the time, monovalent serogroup C conjugate vaccines were the only vaccines available for young children. The objectives to achieve this goal were to prevent outbreaks caused by virulent strains of serogroup C, and achieve sustained reduction of the disease. To achieve these objectives, it was recommended that age-appropriate immunization coverage with the meningococcal C conjugate vaccine be maintained in 97% of children by their 2nd birthday and in 90% of adolescents by their 17th birthday. Today, programs implemented in all P/Ts include immunization of young children with one, two or three doses of serogroup C meningococcal conjugate vaccine and a single booster dose of serogroup C meningococcal conjugate vaccine or quadrivalent ACYW vaccine for adolescents.<sup>88</sup> The gradual implementation of these programs has, to a large extent, helped achieve the goal set out at the national conference on vaccine-preventable diseases.<sup>10</sup>

The epidemiological characteristics of meningococcal infections differ among serogroups, between geographic regions and over time.<sup>89,90</sup> The objectives of a possible immunization program using a new meningococcal vaccine should therefore be adapted to the current epidemiology, and reflect the vaccine strategy.

Given Canada's prevailing epidemiological situation, the main objective of a 4CMenB immunization program would be to reduce, as much as possible, the burden of invasive infections caused by serogroup B strains in terms of frequency of cases, death and survivors with sequelae.

Another objective is to prevent outbreaks or epidemics associated with virulent meningococcal clones not covered by the conjugate vaccines already in use. However, virulent clones exist within serogroups A, B, W135, Y and X, and outbreaks or epidemics caused by clones in these serogroups have been documented in other countries, although not all are endemic to Canada.<sup>89</sup>

A third objective is to prevent sporadic cases of meningococcal infection, which may arise in people at a higher risk, including those in close contact with sick individuals, laboratory workers and persons with certain immune deficiencies.<sup>92</sup>

Reducing Canadians' anxiety about unpredictable illness—which mainly affects healthy children and adolescents, develops rapidly, involves an increased risk of death or sequelae and may lead to secondary cases or outbreaks—can be considered a benefit of an immunization program that succeeds in significantly reducing the prevalence of invasive meningococcal infections. However, reducing the use and cost of health services cannot be considered a primary objective for a program targeting a serious disease characterized by a low incidence and no relatively benign clinical form, as is the case for pneumococcal disease.<sup>93</sup> This observation puts into perspective the importance of the economic efficiency criterion in terms of the health system as part of the decision-making process surrounding this vaccine.

A list of possible objectives for the multicomponent meningococcal B vaccine immunization program can be found in [Table 5](#) (see *Immunization Schedules*).

#### **Strategies for Use of the 4CMenB Vaccine**

The incidence of serogroup B IMD is highest among children under 1 year of age, particularly under 6 months of age, with a second smaller peak in adolescence.<sup>6</sup>

To maximize the direct protection offered by a vaccine, immunization must be started as early as possible, that is, at 2 months of age. Starting to immunize later, at 6 months or a year, would be a more economical solution in terms of doses, but would have the disadvantage of not covering the most at-risk age group. However, this strategy could be considered if a program succeeded in inducing herd immunity, which would provide indirect protection to infants. To protect adolescent individuals directly, it would be advisable to start immunizations between the ages of 12 and 14 years. Both approaches (newborns + adolescents) may be combined, as is currently done to prevent serogroup C invasive infections in Canada.

The immunogenicity data available for the 4CMenB vaccine (published and unpublished) indicates that antibody titres decline over time in both children and adolescents.<sup>95</sup> This very likely means that the direct clinical protection provided by the 4CMen B vaccine diminishes over time. This same phenomenon of waning immunity has been observed with polysaccharide conjugate vaccines for serogroup C however, the duration of protection from the 4CMenB vaccine is completely unknown and difficult to predict from studies of conjugate vaccines as the vaccines are so different. However, this does occur more gradually in adolescents and young children compared with infants.<sup>9,96</sup>

A conjugate vaccine immunization program providing only short-term direct protection would have only a limited impact on the burden of IMD. If the vaccine is effective in reducing the prevalence of carriage of *N. meningitidis*, thereby reducing the spread of pathogenic bacteria among the general population and indirectly protecting vulnerable individuals through herd immunity, this burden could be significantly reduced. Such a strategy seems possible only with adolescent immunization, since the prevalence of carriage peaks in the 15–24 age group.<sup>97</sup> An



accurate analysis of the propagation of the ST269 clone in Québec over the past 10 years indicates that adolescents and young adults were the first to be affected, and that the clone subsequently spread to young children and older adults.<sup>94</sup> Achieving and maintaining high immunization coverage in adolescents seems to be the preferred strategy to hopefully provide indirect protection for long-term interruption of the circulation of the bacterial clones covered by the vaccine and provide long-term protection for the entire population.

The effectiveness of the serogroup C conjugate vaccine in reducing the prevalence of carriage following a mass immunization campaign is proven.<sup>98</sup> Unpublished data from a randomized trial conducted with students in the United Kingdom using the 4CMenB vaccine suggests an effect on acquisition (probably not on duration) of carriage of sensitive strains from all serogroups.<sup>95</sup> However, the effect could be to a lesser extent than that observed with the serogroup C conjugate vaccine. In both the United Kingdom and Québec, intense and long-lasting (more than 10 years) herd immunity was induced after a mass immunization campaigns with MenC vaccines that reached nearly 80% of youth, followed by routine immunization of children with a conjugate vaccine.<sup>9,96</sup> It is known that meningococcal bacteria are not highly transmittable. For all serogroup C strains, the basic reproduction number (i.e. the average number of individuals likely to be infected by a carrier in a non-immune population) has been estimated at 1.4.<sup>99</sup> The basic reproduction number is likely lower for serogroup B than for serogroup C.<sup>100</sup> In this context, even a modest effect of the vaccine on the spread of meningococcal disease in the population could, over the long term, result in a dramatic decrease in carriage, or even elimination, of clones covered by the vaccine. This type of scenario is predicted in two dynamic simulation models.<sup>95,101</sup>

An immunization program focused solely on adolescents could be more cost-effective in the long term than a program that combines child and adolescent immunization. This hypothesis is supported by the results of dynamic simulation models.<sup>95,101</sup> An adolescent-focused program has the significant disadvantage of relying entirely on potential herd immunity, which could take several years to be fully realized. A program that combines child and adolescent immunization therefore seems prudent and more appealing to rapidly decrease the burden of this illness in young children, even if it is more costly and potentially less cost-effective.

Conjugate meningococcal vaccines prepared from outer membrane vesicles (OMV) were used with varying success to control outbreaks caused by certain clones in serogroup B.<sup>102</sup> How quickly the immunization program is implemented, the coverage rates achieved and the similarity between the epidemic clone and vaccine strain are the factors that determine the effectiveness of such interventions. One of the major problems for controlling outbreaks caused by a virulent strain of meningococcal disease is defining the affected population (geographical area or community defined by institutional link) and determining the intervention threshold. The epidemiology of meningococcal infections is highly unpredictable, and healthy carriers are much more common than cases of invasive infection. In

Québec in the early 1990s, numerous outbreaks caused by a virulent clone of serogroup C could not be controlled by targeted immunization, and mass immunization ultimately had to be used to control the situation.<sup>14</sup>

Routinely immunizing people at high-risk of infection with conjugate meningococcal vaccines is recommended in Canada, and target groups were defined in the most recent statement from NACI.<sup>92</sup> 4CMenB could be offered to the same groups under the same circumstances in accordance with the 4CMenB immunization schedule.

### Replacement Risk

In the United Kingdom, following the implementation in 1999–2000 of a mass staged infant, toddler and youth immunization program with a serogroup C conjugate meningococcal vaccine, a reduction from 0.5% to 0.2% in the prevalence of carriage of serogroup C strains was noted, without a reduction in the overall prevalence of carriage of *N. meningitidis*, and some experts flagged the possibility of the existence of a serogroup replacement.<sup>104</sup> Several mechanisms can explain the replacement: the simple occupation of an empty ecological niche by strains not covered by the vaccine or the induction of the emergence of new clones due to the modification of the genes controlling the chemical composition of the capsular polysaccharide (capsule switching). After the mass immunization campaign with a serogroup C conjugate meningococcal vaccine in Québec, there was an emergence of a MenB strain characterized as B:17:P1.19 ST-269 responsible for most of the IMD reported in the province.<sup>105</sup> For serogroup C, the replacement phenomenon had no marked epidemiological consequences owing to the low percentage of serogroup carriers in the general population.<sup>104</sup> This could change with the use of the 4CMenB vaccine, which may considerably reduce the percentage of carriers of all *N. meningitidis* strains in the adolescents and young adults that make up the transmission reservoir.<sup>97</sup> For this reason, it will be important to monitor the incidence of invasive infections caused by all encapsulated bacteria following the implementation of a meningococcal B vaccine immunization program and to complete, if possible, studies to assess the impact on nasopharyngeal carriage of the bacteria.

### Schedule

#### Immunization Schedules

The immunization program using the 4CMenB vaccine should be implemented according to approved schedules. No data are currently available to justify reducing the number of doses recommended by the manufacturer. However, it is possible to reduce the number of doses in adolescents (from two to one) when cohorts vaccinated at a young age reach the age for a booster dose in adolescence. That argument is based on the experience gained from all conjugate vaccines in the immunization schedules. Along the same lines, primary immunization in children could be delayed if invasive serogroup B meningococcal infections were under control for an extended period in the entire population as a result of herd immunity.

Such a strategy was successfully employed in Québec with the serogroup C conjugate meningococcal vaccine; the age of primary immunization was increased to 12 months following a mass immunization campaign.<sup>9</sup>

[Table 5](#) lists schedules that could be considered in Canada. Note that the lack of information about direct and indirect clinical efficacy of the vaccine makes it difficult to quantify objectives for reducing the burden of the disease.

**Table 5 - Objectives and Schedules for a Multicomponent Meningococcal B (4CMenB) Immunization Program in Canada**

Health and societal objectives
<ol style="list-style-type: none"> <li>1. Reduce burden of invasive meningococcal serogroup B in terms of frequency of cases, death and sequelae.</li> <li>2. Prevent outbreaks caused by a virulent clone covered by 4CMenB vaccine.</li> <li>3. Prevent a maximum number of cases of invasive meningococcal infections caused by a virulent clone covered by 4CMenB vaccine, in people at a higher risk of contracting the illness based on specific exposure or medical conditions.</li> <li>4. Minimize the anxiety and media coverage associated with sporadic cases and outbreaks of invasive meningococcal infections in the population.</li> </ol>
Schedules
<ol style="list-style-type: none"> <li>1. Primary immunization of young children. <ol style="list-style-type: none"> <li>1.1. Early immunization: 4 doses of vaccine offered, respectively, at 2, 4, 6, and 12–18 months (minimum one month interval between each dose).</li> <li>1.2. Late immunization: 3 doses of vaccine, the first two offered between 6 and 12 months and a booster dose during the 2nd year (minimum 2-month interval between each dose).</li> </ol> </li> <li>2. Immunization of Adolescents. <ol style="list-style-type: none"> <li>2.1. Primary immunization: 2 doses of vaccine offered between ages 12 and 14 years (minimum 2-month interval between doses).</li> <li>2.2. Booster immunization: 1 dose of vaccine offered between ages 12 and 14 years (to be confirmed by future studies).</li> </ol> </li> </ol>

### Immunization coverage objectives

1. Age-appropriate coverage in 90% of children before their 2nd birthday.
2. Age-appropriate coverage in 80% of adolescents before their 17th birthday.

### *Introduction of Conjugate Vaccine With or Without Catch-Up*

Herd immunity, which has yet to be proven, could possibly be induced by the 4CMenB vaccine administered as part of a routine immunization for adolescents with or without catch-up. Dynamic simulation models predict that herd immunity would be achieved more quickly if catch-up immunizations were administered in all adolescents.<sup>95,101</sup> However, the advantages of a catch-up campaign in terms of reducing the incidence of disease are short lived. The cost of a catch-up campaign is also an issue since it would need to be done at a separate health care visit. It would increase the workload for vaccinators and primary prevention services. During a meeting of the Comité sur l'immunisation du Québec (CIQ), representatives of pediatrics, family medicine, nurses and healthcare facilities expressed reservations regarding this scenario. Lastly, it is important to consider that there is great uncertainty about the potential coverage of catch-up immunizations in both preschool-aged children and youth between the ages of 15 and 20 years in the context of an endemic disease and low media attention of the illness.

### *National, Provincial or Regional Strategy*

Epidemiological data produced by the Agency highlight the significant differences in incidence of serogroup B *N. meningitidis* between provinces.<sup>8</sup> These differences could be attributed to a variety of factors: actual epidemiological differences, the quality of the surveillance system, the date and method of conjugate immunization program implementation, and random variations. The extent of these types of variations is enough to result in differences of nearly 100 in the cost-effectiveness ratio of a program using 4CMenB vaccine. It is therefore likely that prioritization will vary widely from one province to another when implementing such a program.

Traditionally, immunization programs have varied considerably from one Canadian province to another in terms of introduction date, schedule and vaccine used, even when targeting the same diseases. However, there is generally great consistency within provinces with some exceptions, notably the largely Aboriginal populations in northern regions. A regional—as opposed to a provincial—program may be warranted for 4CMenB should a unique and potentially long-term epidemiological situation arise in an area of a province or territory.

## Social and Economic Costs and Benefits

### Impact, Cost, and Cost-Effectiveness of Various Immunization Strategies

Given the lack of empirical data on the real costs and benefits of an immunization program using 4CMenB, mathematical models must be developed and simulations conducted to study the consequences of various scenarios. From international and national sources, four known simulation models were reviewed, two of which were publications (Pouwels et al.; Christensen et al.) and two were communicated confidentially, one of which from the manufacturer of the 4CMenB vaccine (Tu et al.; Novartis) to the MBPPTG.<sup>95,101,106,107</sup> As a cautionary measure, we searched three databases (PubMed, Embase and Cochrane) on September 1, 2013, using non-specific keywords ("meningo\*" or "meningitis" and "economics" or "model" or "simulation"). No other pertinent references were found aside from those that were already known. It should be noted that the models that have been specifically developed for the Canadian context are the two mentioned above that are not (yet) published.

### Characteristics of the Simulation Models

The main characteristics of the four models that were analyzed are listed in [Table 6](#). A model's primary characteristic is its type. In a Markov cohort model, a population of newborns will grow older and, at each age, there is a probability of IMD with its attendant consequences: death or survival with or without sequelae. The timeline is generally an entire lifetime (about 100 years). The model is calibrated to recalculate the reference population's life expectancy at each age and the incidence of the disease by age. Immunization will lead to a reduction in the risk of disease. The major advantage of such models is their simplicity, which makes them transparent and comprehensible to most decision-makers. They are useful for predicting the impact of vaccines that do not produce herd immunity and for endemic diseases. We can hypothesize that invasive serogroup B meningococcal infections have an endemic or hyperendemic disease profile without the occurrence of major epidemics. However, 4CMenB vaccine may produce herd immunity. The results of the carriage study conducted in Great Britain with the 4CMenB vaccine, though still preliminary, suggest the existence of a herd immunity effect that would not be limited to serogroup B, though the extent and speed of its development cannot be precisely predicted.<sup>95</sup> A recent study conducted in France with another vaccine prepared from OMVs suggests the existence of a very large effect on the carriage of all meningococcal strains.<sup>108</sup> A dynamic model is required to make predictions in such situations. In a dynamic model, the likelihood of infection (the probability that a non-immune person meets a carrier, is infected, and becomes a carrier) varies over time based on the prevalence of carriage among the people with whom that person is in contact.<sup>109</sup>

Dynamic models have a number of advantages over static cohort models, but they also have challenges and limitations. A dynamic model applied to an entire population allows the dynamics of a vaccine's introduction to be represented until a state of equilibrium is reached, which can take several decades. This leads to the

production of much more realistic cost-effectiveness ratios than those generated by a static model, which can only reproduce the equilibrium. In a dynamic model that incorporates a number of states, including susceptible individuals, immune individuals, carriers and non-carriers, the effect of herd immunity is simulated based on empirical data from carriage studies and, possibly, serological studies. Conversely, in a static model, an indirect effect must be the subject of a theoretical assumption (i.e. the indirect effect of a vaccine on the incidence of invasive infections is equal to its effect on the prevalence of carriage). In general, dynamic models are hard for laypeople to understand, and the determination of parameters (estimating the value of parameters that must be approximated by the simulation) is often obscure and difficult to reproduce without the model and the required mathematical background. Since several parameters must be estimated simultaneously by solving systems of equations and adjusting the results to the empirical data concerning prevalence of carriage and disease incidence by age in the population, it is possible for several solutions to produce acceptable results, though only one set of parameters is ultimately accepted.

Another issue is the suitability of the compartmental model, which is necessarily simplistic, to the biological complexity of meningococcal infections. In the two dynamic models that were analyzed, all the clones covered by the vaccine were grouped together, since the vaccine's effect could vary based on the genotype and phenotype of each clone. The immunity induced by asymptomatic carriage is not taken into account, and immunity induced by the vaccine is dichotomous (present or absent), though it could gradually vary. There is a great deal of uncertainty about the average duration of meningococcal carriage. The available studies tend to overestimate these durations due to the lack of sensitivity in identification methods and the long delays between samples. Finally, the two dynamic models do not account for a state of simultaneous carriage of different strains, interaction between different strains or a possible replacement phenomenon, points that if considered could help assess the benefits of a program.<sup>110</sup>

One of the fundamental principles of conducting economic analyses is to include all plausible scenarios for the use of a vaccine.<sup>111</sup> In this case, this means a scenario where vaccine is not used, an infant immunization program with or without catch-up, an adolescent immunization program with or without catch-up, or a program simultaneously targeting infants and adolescents with or without catch-up. Some such scenarios are found in the two dynamic models that were analyzed (Christensen et al.; Novartis) but not in the two static models (Pouwels et al.; Tu et al.).<sup>95,101,106,107</sup>

An economic assessment should ideally adopt a societal point of view and , include the program's consequences for the health system, families and society.<sup>111,112</sup> In all the models analyzed, the main direct costs of the disease are taken into account, aside from the cost of managing outbreaks that can occasionally occur in closed environments or small communities. It is reasonable to take into account a loss of



quality of life for the informal caregivers of a patient suffering from permanent, serious sequelae. However, accounting for the lost productivity associated with early deaths and sequelae is debatable for some.<sup>111-113</sup> Loss of quality of life for individuals (which appears in the denominator of a cost-effectiveness ratio) can be considered a distinct element of lost productivity for a society (which appears in the ratio's numerator). The opposite can be argued with reference to the principle of avoiding double inclusion of the same element in the numerator and the denominator.

Among the most important parameters that determine the values of the cost-effectiveness ratios are disease incidence, case fatality ratio, and prevalence of permanent sequelae for survivors. However, there is relative certainty about the values of these parameters.

One factor that strongly influences the cost-effectiveness ratios of an immunization program is the discount rate, which applies future costs and benefits to the present value.<sup>115</sup> Since most of a program's costs arise during the vaccination of a young infant or an adolescent, and most of the benefits (in terms of increased life expectancy and reduced use of health services) are distributed over several decades, the World Health Organization advocates for a relatively low rate for all elements (e.g. 3%), a rate that decreases over time.<sup>112</sup> Another approach that is becoming increasingly popular is the adoption of different discount rates for financial and health elements (e.g. 1.5% and 3.5%).<sup>115</sup> Higher rates (e.g. 5%) are suggested by some agencies, which largely analyze diagnostic techniques and medical or surgical treatments for which the benefits are gained soon after intervention.<sup>116</sup> Such a practice would terminate most immunization programs for diseases that are fatal or disabling at a young age.<sup>117</sup>

There are major differences between countries when it comes to the incidence of IMD, vaccine prices, and health service costs. This makes it risky to extrapolate results from economic studies conducted in a European context to a Canadian one. There is less variation within Canada in terms of vaccine prices and health service costs. However, there can be substantial differences in disease incidence and the cost of administering vaccines, depending on whether vaccination services are offered predominantly by the public health infrastructure or through individual health providers' offices.

**Table 6 – Structure and Main Characteristics of Each Model**

Characteristics	Netherlands model (Pouwels et al. 2013)	Ontario model (Tu et al., unpublished)	British model (Christensen et al. 2013)	Novartis model (Novartis, unpublished)
Type of model	Markov, population, deterministic, and static.	Markov, population, deterministic, and static.	Compartmental, transitional, population, probabilistic, and static or dynamic.	Compartmental, transitional, population, probabilistic, dynamic.
Context	Netherlands	Ontario	United Kingdom	Canada, Ontario, Québec, high incidence in Québec
Population	Cohort of 185 000 births with age-specific mortality.	Cohort of 150 000 births with age-specific mortality.	Cohort of 708 000 births in England and Wales and population's age structure in 2008.	Stationary population representing that of Canada (34 880 500), Ontario (13 515 900) and Québec (8 054 800) in 2012.
Timeline	99 years	A lifetime ( $\approx 100$ years)	100 years	100 years
Age categories	One-month time steps until 23 months, then one year.	One-year time steps.	One-month time steps in the cohort model.  One-day cycles in the dynamic model.	Cycles of one hundredth of a month in the dynamic model and one-month compartments (100 cycles).
Etiological model	Healthy-sick-deceased or sequelae or unharmed.	Healthy-sick-deceased or sequelae or unharmed.	Healthy-sick-deceased or sequelae or unharmed in the cohort model.  9 states in the dynamic model: susceptible non-carrier, carrier of a vaccinal strain, carrier of another strain; each of these 3 categories can move to an immune state after vaccination and lose vaccinal protection. A vaccinated, protected individual has a lower probability of becoming a carrier	9 states in a dynamic model: susceptible non-carrier, vaccinated or not; carrier of a vaccinal strain, vaccinated or not; carrier of another strain, vaccinated or not; protected, vaccinated non-carrier; protected, vaccinated carrier of a vaccinal strain; protected, vaccinated carrier of another strain; individual sick from non-vaccinal strain; individual sick from non-vaccinal strain; deceased. A vaccinated and immune individual



Characteristics	Netherlands model (Pouwels et al. 2013)	Ontario model (Tu et al., unpublished)	British model (Christensen et al. 2013)	Novartis model (Novartis, unpublished)
Etiological model			and getting sick from a vaccinal strain.	has a low probability of becoming a carrier and getting sick from a vaccinal strain.
Parameterization of the model	Reproduce the disease's incidence by age without vaccination.	Reproduce the disease's incidence by age without vaccination.	Reproduce the disease's prevalence of carriage and incidence by age without vaccination, with an interpersonal contact matrix.	Reproduce the disease's prevalence of carriage and incidence by age without vaccination, with an interpersonal contact matrix.
Perspective	Social cost-utility (health system and families).	Taxpayer cost-utility (health system).	Taxpayer cost-utility (health system).	Social cost-utility (health system, families, and society).
Programs considered	Immunization of newborns with 4 doses (+possible booster at 12 years).	Immunization of newborns with 4 doses.	7 scenarios for immunization of newborns (3 or 4 doses) and/or adolescents (3 doses) with or without catch-up.	Immunization of newborns (4 doses) and immunization of newborns (4 doses) with immunization of adolescents (2 doses for naive individuals and only 1 dose for those already vaccinated).
Target population vaccinal coverage	95%	97%	91%	85% for children and 80% for adolescents
Burden of disease	Invasive serogroup B meningococcal infections confirmed by laboratory.	Invasive serogroup B meningococcal infections confirmed by laboratory.	Invasive meningococcal infections of all serogroups confirmed by laboratory.	Invasive meningococcal infections of all serogroups confirmed by laboratory, covered and not covered by the vaccine.
Base incidence	All ages: 1.10/100 000 person-years	All ages: 0.19/100 000 person-years	All ages: 3.17/100 000 person-years	All ages /100 000 person-years Canada: 0.76 Ontario: 0.58 Québec: 1.16 Québec high: 2.32
Fatality ratio	5.4%	10.7%	4.0%	Canada: 8.1% Ontario: 13.4% Québec: 5.3%

Characteristics	Netherlands model (Pouwels et al. 2013)	Ontario model (Tu et al., unpublished)	British model (Christensen et al. 2013)	Novartis model (Novartis, unpublished)
Adjustment for under-reporting	Yes: 15%	No	No	Yes: 25%
Direct costs of the disease	Treatment of episodes and sequelae. Specialized education and institutionalization for survivors with sequelae.	Treatment of episodes and sequelae. Prophylaxis for contacts.	Treatment of episodes and sequelae. Specialized education and institutionalization for survivors with sequelae. Prophylaxis for contacts.	Treatment of episodes and sequelae. Specialized education and institutionalization for survivors with sequelae.
Lost quality of life	Patients with sequelae.	Patients with sequelae and informal caregivers.	Patients with sequelae.	Patients with sequelae and informal caregivers.
Indirect costs of the disease	Absenteeism of parents and sick individuals via the friction-cost method. Lost productivity associated with deaths and sequelae not taken into account.	Not taken into account.	Not taken into account.	Lost productivity via the capital-human method associated with deaths and sequelae taken into account, including losses associated with a 6.4 point IQ decrease in 81.1% of survivors.
Types of program costs	Purchase and administration of vaccines. Undesirable treatment effects.	Purchase and administration of vaccines. Undesirable treatment effects.	Purchase and administration of vaccines. Undesirable treatment effects.	Purchase and administration of vaccines. Undesirable treatment effects.
Direct vaccine efficacy	Maximum 75% against serogroup B meningococcus, with progressive loss over time.	Maximum 59% (90% efficacy x 66% MATS coverage of strains) against serogroup B meningococcus over 10 years.	Maximum 75% in children and 80% in adolescents against all meningococcus with an average protection duration between 18 and 48 months for children and 120 months for adolescents.	Canada: Maximum of 59% (98–99% efficacy x 60% MATS coverage of strains), 4 doses for children and 2 doses for adolescents with a decrease of 1/60 per month for children and 1/120 per month for adolescents.
Indirect vaccine efficacy	Not taken into account.	Not taken into account.	Protection against acquisition of carriage: 60%.	Protection against acquisition of carriage: 30% and 60%.
Monetary unit	2009 EUR	2012 CAD	2008 GBP	2012 CAD

Characteristics	Netherlands model (Pouwels et al. 2013)	Ontario model (Tu et al., unpublished)	British model (Christensen et al. 2013)	Novartis model (Novartis, unpublished)
Vaccine cost (base)	40.00 EUR (56.00 CAD)	90.00 CAD	40.00 GBP (65.00 CAD)	60.00 CAD
Cost of administration per dose	8.81 EUR (9.50 CAD)	4.50 CAD	5.00 GBP (8.10 CAD)	9.00 CAD
Cost-effectiveness ratio	EUR/incremental QALY (net cost of strategy divided by QALY gained)	CAD/incremental QALY (net cost of strategy divided by QALY gained)	GBP/incremental QALY (net cost of strategy divided by QALY gained)	CAD/incremental QALY (net cost of strategy divided by QALY gained)
Discount	Financial elements = 4.0% Health elements = 1.5%	Financial elements = 5.0% Health elements = 5.0%	Financial and health elements: 3.5% during years 0–30, 3.0% during years 31–75, 2.5% thereafter	Financial elements = 3.0% and 3.5% Health elements = 3.0% and 1.5%
Sensitivity analyses	Univariate, bivariate, and multivariate (Monte Carlo).	Univariate and bivariate.	Univariate, bivariate, and multivariate (Monte Carlo).	Univariate
Cost-effectiveness thresholds	Very favorable: $\leq 20,000$ EUR/QALY Acceptable: $\leq 50,000$ EUR/QALY	Not specified	Acceptable: $\leq 30,000$ GBP/QALY (49,000 CAD)	Not specified
External validation of the model	No	No	No	Yes, by reference to the British model.

### ***Impact of the Various Strategies on the Burden of Disease***

As anticipated, the two statistical models that do not incorporate a herd immunity effect predict little decrease in the incidence of IMD identified in the entire population (between 14% and 18%) ([Table 7](#)). The total number of prevented cases is higher in the Netherlands model than in the Ontario model, because it takes into account the effect of the vaccine on all meningococcal infections and because of the higher disease incidence in Europe.<sup>106,107</sup> In the Ontario model, herd immunity is simulated by assuming that vaccine protection will last for life.<sup>107</sup> Such an assumption does not match the real effect of herd immunity, which applies to the whole population, not just vaccinated individuals. However, it is unlikely that immunization of young children would lead to the development of significant herd immunity, as shown in the simulations from the dynamic models.<sup>95,101</sup>

**Table 7 - Health Impact of Baseline Scenarios in the Various Models**

Model	Effect of program in terms of reducing the burden of disease
Netherlands model (Pouwels et al. 2013)	Baseline model: Immunization of newborns with 4 doses: Reduction in number of serogroup B cases in the cohort by 14% (39/276).
	Baseline model: Immunization of newborns with 4 doses: Reduction in number of serogroup B cases in the cohort by 18% (51/276).
Ontario model (Tu et al., unpublished)	Baseline model: Immunization of newborns with 4 doses: Reduction in number of serogroup B cases in the cohort by 16% (3.68/23.04). Based on scenarios: 16% to 78%.
British model (Christensen et al. 2013)	Baseline cohort model: Immunization of newborns with 4 doses: Reduction in number of serogroup B cases in the cohort by 27% (484/1799). Based on scenarios: 19% to 28%.
	Baseline dynamic model: Immunization of newborns with 4 doses: Reduction in number of cases in the cohort by 44% for all serogroups, 5 to 10 years after the program's initiation. Catch-up for cohorts aged 5 to 17 maximizes burden reduction.
	Baseline dynamic model: Immunization of newborns with 3 doses: Reduction in number of cases in the cohort by 94% for all serogroups, 90 years after the program's initiation.
Novartis model (Novartis, unpublished)	Baseline dynamic model for Canada: Immunization of newborns with 4 doses: Reduction in number of cases in the population by 20% for all serogroups, 30 years after the program's initiation. Based on scenarios: 20% to 38%.
	Baseline dynamic model for Canada: Immunization of newborns with 4 doses: Reduction of number of cases in the population by 50–60% for all serogroups, 40 years after the program's initiation.

The British model developed for 4CMenB came directly from the one developed for serogroup C conjugate polysaccharide vaccines, whose predictive capacity was successfully tested.<sup>96,99,101,118</sup> In that model, the routine immunization of young children eventually led to a global decrease of 40% in the incidence of IMD. It takes between 5 and 40 years to reach that equilibrium, based on modelling scenarios. A catch-up program including children up to 5 years of age helps to very quickly reduce the disease incidence in young children, but the benefit of the catch-up program and the accompanying herd immunity is short-lived. Conversely, a program targeted only at adolescents' takes effect more slowly, but in the very long term leads to near-elimination of the strains covered by the vaccine because of loss of carriers of the bacteria.

The dynamic model developed by Novartis is based on the same principles as the British model, though the compartmental structure is slightly different.<sup>95,101</sup> The two models' predictions were compared using the same epidemiological parameters.<sup>95</sup> The conclusion was that the incidence of covered strains decreased more rapidly and to a greater extent in the first model (final reduction of 94% in the British

model and 83% in the Novartis model). It appears that the difference can mainly be explained by the differing contact matrices; Novartis used Mossong's, which produced less extensive herd immunity than the one used in the British model.<sup>119</sup> The Novartis model that offered predictions based on a decrease of 33% (as opposed to 66%) in the probability of nasopharyngeal infection associated with vaccine-derived immunity. Because of this, the predictions concerning the vaccine's impact were more conservative than those in the British model, given the initial results of the carriage study with the 4CMenB vaccine.<sup>95</sup> In the Novartis model, the results of various scenarios in terms of the absolute number of prevented cases is proportional to the base incidence of meningococcal infections in the population and the proportion of strains potentially covered by the vaccine, which could differ from one province to another ([Table 7](#)).

### *Cost of Various Strategies*

The cost of an immunization program has four facets: the cost of the vaccine, the cost of administration, the cost of managing the program and, finally, the cost of implementation. Only the first two facets were taken into account in the economic analyses for the 4CMenB vaccine.

It is difficult to predict the price at which the new vaccine will be offered to jurisdictions that would like to establish a forward contract or under the Federal/Provincial/Territorial procurement process. In the economic study conducted for Ontario, a reference price of 90 CAD was selected based on the price of other newly implemented vaccines included in Canadian immunization programs.<sup>107</sup> In the economic study conducted in the United Kingdom, the reference price was 40 GBP or 65 CAD.<sup>101</sup> In the Netherlands study, the reference price was 40 EUR or 56 CAD.<sup>106</sup> The purchase price was treated as a discrete variable with limits in Novartis's analysis, which is acceptable in a context of uncertainty. However, a reference price of 60 CAD per dose was chosen in the baseline scenarios. [Tables 8](#) to [11](#) indicate the potential total purchase cost for each province or territory for annual routine immunization of infants (4 doses) and catch-up immunization of youth aged 12 to 19 years (2 doses, excluding a cohort vaccinated through routine immunization). Coverage for young children and adolescents was assumed at 90% and 80%, respectively, based on immunization program performance in Québec.<sup>120,121</sup> The total initial investment for a full program in Canada would be between 375 million CAD (40 CAD per dose) and 750 million CAD (80 CAD per dose), amounts never reached previously for an immunization program.

**Table 8 – Purchase Cost of Conjugate Meningococcal Vaccine for Immunization of a Cohort of Births per Province (x \$1000)**

Provinces and territories	Births ¥	Number of doses *	\$40/dose	\$60/dose	\$80/dose
Newfoundland and Labrador	4823	17 363	\$695	\$1,042	\$1,389
Prince Edward Island	1420	5112	\$204	\$307	\$409
Nova Scotia	8848	31 853	\$1,274	\$1,911	\$2,548
New Brunswick	7 313	26 327	\$1,053	\$1,580	\$2,106
Québec	88 500	318 600	\$12,744	\$19,116	\$25,488
Ontario	141 799	510 476	\$20,419	\$30,629	\$40,838
Manitoba	16 250	58 500	\$2,340	\$3,510	\$4,680
Saskatchewan	14 801	53 284	\$2,131	\$3,197	\$4,263
Alberta	52 243	188 075	\$7,523	\$11,284	\$15,046
British Columbia	43 677	157 237	\$6,289	\$9,434	\$12,579
Yukon	383	1 379	\$55	\$83	\$110
Northwest Territories	706	2 542	\$102	\$152	\$203
Nunavut	835	3 006	\$120	\$180	\$240
<b>Canada</b>	<b>381 598</b>	<b>1 373 754</b>	<b>\$54,949</b>	<b>\$82,425</b>	<b>\$109,899</b>

¥ 2012 estimate; \* 4 doses per person and 90% immunization coverage

**Table 9 – Purchase Cost of Conjugate Meningococcal Vaccine for Catch-up Immunization of Children Aged 1 to 4 per Province (x \$1,000)**

Provinces and territories	Population 1–4 years ¥	Number of doses *	\$40/dose	\$60/dose	\$80/dose
Newfoundland and Labrador	19 954	35 917	\$1,437	\$2,155	\$2,873
Prince Edward Island	5 748	10 346	\$413	\$621	\$828
Nova Scotia	36 856	66 341	\$2,654	\$3,980	\$5,307
New Brunswick	29 846	53 723	\$2,148	\$3,223	\$4,298
Québec	358 531	645 356	\$25,814	\$38,721	\$51,628
Ontario	574 242	1 033 636	\$41,345	\$62,018	\$82,691
Manitoba	64 612	116 302	\$4,652	\$6,978	\$9,304
Saskatchewan	58 541	105 374	\$4,215	\$6,322	\$8,430
Alberta	206 838	372 308	\$14,892	\$22,339	\$29,785
British Columbia	180 875	325 575	\$13,023	\$19,535	\$26,046
Yukon	1 599	2 878	\$115	\$173	\$230
Northwest Territories	2 472	4 450	\$178	\$267	\$356
Nunavut	3 097	5 575	\$223	\$334	\$446
<b>Canada</b>	<b>1 543 211</b>	<b>2 777 781</b>	<b>\$111,109</b>	<b>\$166,666</b>	<b>\$222,222</b>

¥ 2012 estimate; \* 2 doses per person and 90% immunization coverage



**Table 10 - Purchase Cost of Conjugate Meningococcal Vaccine for Immunization of a Cohort of Adolescents per Province (x \$1,000)**

Provinces and territories	Population 12 years ¥	Number of doses *	\$40/dose	\$60/dose	\$80/dose
Newfoundland and Labrador	5 300	8 480	\$339	\$509	\$678
Prince Edward Island	1 659	2 654	\$106	\$159	\$212
Nova Scotia	9 214	14 742	\$589	\$885	\$1,179
New Brunswick	7 854	12 566	\$502	\$754	\$1,005
Québec	79 877	127 803	\$5,112	\$7,668	\$10,224
Ontario	149 940	239 904	\$9,596	\$14,394	\$19,192
Manitoba	15 934	25 494	\$1,019	\$1,530	\$2,040
Saskatchewan	13 294	21 270	\$850	\$1,276	\$1,702
Alberta	43 772	70 035	\$2,801	\$4,202	\$5,603
British Columbia	46 605	74 568	\$2,982	\$4,474	\$5,965
Yukon	406	650	\$26	\$39	\$52
Northwest Territories	618	989	\$439	\$59	\$79
Nunavut	685	1 096	\$43	\$66	\$88
<b>Canada</b>	<b>375 158</b>	<b>600 251</b>	<b>\$24,004</b>	<b>\$36,015</b>	<b>\$48,019</b>

¥ 2012 estimate; \* 2 doses per person and 80% immunization coverage

**Table 11 - Purchase Cost of Conjugate Meningococcal Vaccine for Catch-up Immunization of Individuals Aged 13 to 19 per Province (x \$1,000)**

Provinces and territories	Population 13-19 years ¥	Number of doses *	\$40/dose	\$60/dose	\$80/dose
Newfoundland and Labrador	39 404	63 046	\$2,522	\$3,783	\$5,044
Prince Edward Island	13 228	21 165	\$529	\$1,270	\$1,693
Nova Scotia	64 498	103 197	\$2,580	\$6,192	\$8,256
New Brunswick	60 269	96 430	\$2,411	\$5,786	\$7,714
Québec	635 194	1 016 310	\$25,408	\$60,979	\$81,305
Ontario	1 162 119	1 859 390	\$46,485	\$111,563	\$148,751
Manitoba	119 756	191 610	\$4,790	\$11,497	\$15,329
Saskatchewan	98 512	157 619	\$3,940	\$9,457	\$12,610
Alberta	326 262	522 019	\$13,050	\$31,321	\$41,762
British Columbia	371 369	594 190	\$14,855	\$35,651	\$47,535
Yukon	2 906	4 650	\$116	\$279	\$372
Northwest Territories	4 326	6 922	\$173	\$415	\$554
Nunavut	4 571	7 314	\$293	\$439	\$585
<b>Canada</b>	<b>2 902 414</b>	<b>4 643 862</b>	<b>\$117,152</b>	<b>\$278,632</b>	<b>\$371,510</b>

¥ 2012 estimate; \* 2 doses per person and 80% immunization coverage

It is relatively difficult to estimate the administration costs of vaccines under a regular immunization program for young children and adolescents, with or without catch-up in Canada. The organization of services and the funding methods vary enormously among provinces and it must be taken into account that including a new vaccine could lead to additional visits, which would increase costs considerably. Informing parents about using acetaminophen to prevent fever will necessarily require further time for explanation by a health care team member. A few options are possible. The cost for the health care system of administering an additional vaccine as part of a routine visit was estimated at 4.50 CAD in Ontario, 8.50 CAD in Québec, and 9.00 CAD in Novartis's economic study.<sup>95,107,122</sup> Based on the time required to administer a vaccine during a visit in which a nurse administers several vaccines, the resulting cost is between 14.77 CAD and 21.12 CAD.<sup>123</sup> An additional visit costs the Québec health care system an estimated 12.00 CAD in a health care centre (CLSC) and 11.50 CAD in a school.<sup>124</sup> Expenses could increase if vaccines are administered in medical clinics with a visit fee.

All new immunization programs involve one-time expenses related to training vaccinators and preparing information material for parents. We do not have any published data on this subject. Implementing an immunization program using a vaccine for which we have only scant information on the uncommon side effects and the clinical effectiveness should necessarily include a comprehensive monitoring-evaluation-research component, which could cost several millions of dollars, based on recent experiences in Québec.

### *Cost-Effectiveness of Various Strategies*

The only two economic analyses relevant to the Canadian context are those conducted for Ontario and Novartis's four contextual studies, both of which are unpublished. The most unfavourable cost-effectiveness ratios are those from the Ontario analysis.<sup>107</sup> In the baseline model, the differential cost of the program per QALY is an estimated \$55.6 million CAD for one cohort ([Table 12](#)). This is explained by the combination of several features of the model: a low disease incidence, a static model that does not take into account in the baseline scenario the existence of herd immunity, a health care system perspective, a high-priced vaccine active against only serogroup B meningococcal disease and a discount of 5% per year. The three factors with the greatest influence on these results are the cost of the vaccine, the incidence of serogroup B invasive infections and the discount. For the cost-effectiveness ratio to be below \$40,000 or \$50,000 per QALY the incidence of meningococcal infections would have to be multiplied by 10, or the cost of the vaccine would have to be almost nil to be cost-effective.<sup>107,125</sup> Herd immunity, which implies a reduction in disease incidence in the entire population (vaccinated and non-vaccinated), occurs very quickly following the implementation of a program once a significant proportion of the adolescents in the reservoir of infection are vaccinated. From then on, the discount cannot be applied to the indirect benefits

derived over the course of an entire lifetime by reducing them to their expected value in the first year of life. Only a dynamic model, applied to a population rather than a cohort, can accurately evaluate the economic consequences of this type of vaccine.

Although unpublished and manufacturer-funded, the model developed by Novartis is very similar to the one developed with an independent team in the United Kingdom that served as a basis (in an improved and unavailable version) for that country's decision process.<sup>101</sup> The challenge with Novartis's model is that it incorporates all the elements of the burden of disease that favour the adoption of the vaccine. The most contentious of these elements is the accounting of lost productivity associated with death and sequelae, particularly the potential slight decrease in IQ for a significant proportion of survivors. Despite this, the cost-effectiveness ratios generated by adopting a discount of 3% are not particularly favourable for a realistic range of selling prices for the vaccine ([Table 13](#)).

From a Canadian societal perspective, the price would have to be equal to or less than \$20 CAD per dose to generate a cost-effectiveness ratio equal to or less than \$100,000 CAD/QALY. Even in Québec, the province with the highest incidence of invasive infections, the selling price would have to be \$35 CAD or less to meet this easily attainable criterion and around \$25 CAD to attain 50,000 CAD/QALY. It is only for high disease incidences like those found in certain regions of Québec that a mixed child + adolescent program could be economically profitable ( $\leq$  \$50,000 CAD/QALY) at a reasonable vaccine cost ( $\leq$  \$60 CAD/dose).<sup>24</sup> However, it is likely that Eastern Québec's current prevailing epidemiological situation will not continue for a century, which is one of the hypotheses of the model.

**Table 12 – Cost-Effectiveness of Baseline Scenarios in the Various Models**

Model	Effect of program in terms of reducing the burden of disease
Netherlands model (Pouwels et al. 2013)	Baseline: Immunization of newborns with 4 doses: €244,000/QALY. Minimum of: €25,000/QALY with free 100%-effective vaccine.
	Baseline: Immunization of newborns with 4 doses + booster at 12 years: €247,000/QALY.
Ontario model (Tu et al. written communication)	Baseline model: Immunization of newborns with 4 doses: 5,589,000 CAD/QALY. Minimum of: 542,000 CAD/QALY with disease incidence that is ten times higher.
British model (Christensen et al. 2013)	Cohort baseline model: Immunization of newborns with 4 doses: 162,000 GBP/QALY. Sensitivity analyses: between 0 and 250,000 CAD/QALY.
	Dynamic baseline model: Immunization of newborns with 4 doses: 96,000 GPB/QALY.
	Dynamic baseline model: Immunization of adolescents with 3 doses: 40,000 GPB/QALY.

Model	Effect of program in terms of reducing the burden of disease
Novartis model (Novartis, written communication)	Dynamic baseline model for Canada: Immunization of newborns with 4 doses: 730,000 CAD/QALY (health care system) and 730,000 CAD/QALY (societal).
	Dynamic baseline model for Canada: Immunization of newborns with 4 doses and adolescents with 2 and then 1 dose: 416,000 CAD/QALY (health care system) and 311,000 CAD/QALY (societal). The cost of the vaccine must be < 20 CAD per dose to generate societal ratios under 100,000 CAD/QALY.

The numerous uncertainties surrounding the clinical performance of 4CMenB and its cost; as well as the future evolution of the disease incidence; combined with simulation models that do not take proper account of the complexity of the etiopathology of IMD; and the lack of consensus on the methodological choices governing economic analyses, make this type of exercise extremely challenging. Results that differ by a factor of over 100 should therefore not be surprising.

For Canada, less favourable results are presented in an analysis conducted from the Ontario health care system's perspective with methodological choices that are relatively unfavourable to the vaccine; whereas the most favourable results are those from the model developed by the pharmaceutical company that produces the vaccine with parameters that are credible, but systematically aligned to minimize the value of marginal cost-effectiveness ratios. Given this uncertainty, conclusive data on the effectiveness of the vaccine and the indirect impacts of a program should be generated and the models should be redone using a stronger basis. In two recent editorials, the importance, relevance and even the ethical nature of economic analyses conducted for new vaccines that are complicated to develop and target rare and serious diseases were contested.<sup>126,127</sup> Though an economic analysis is indispensable in a decision-making process that involves considerable financial investment, there is a need for objective, independent modelling to assess the cost effectiveness of 4CMenB for Canada.

## Feasibility and Acceptability

### *Acceptability of Vaccination Against Serogroup B Meningococcus*

Except for a vaccine developed specifically for vaccination in the event of an epidemic (used in New Zealand and France), no vaccine against all strains of serogroup B meningococci is currently available. Although the Canadian population is generally in favour of vaccination, several studies have shown that parents lack knowledge about this subject and that there is an increase in negative attitudes toward vaccination.<sup>128-131</sup> Indeed, acceptability of a new vaccine against serogroup B meningococci should not be taken for granted. However, results of Canadian studies conducted in the early 2000s indicated that meningitis was one of the diseases that most worried parents.<sup>132,133</sup> Estimates of serogroup C meningococcus vaccine coverage also indicate that this vaccination is well-accepted by the population.<sup>134</sup>

Only few studies on the acceptability of vaccination against serogroup B meningococcus among the population and health professionals have been identified.<sup>135-142</sup> Most of these studies were conducted with population groups that were unfamiliar with or knew very few of the characteristics of meningococcus protein vaccines, including their side effects (e.g. pyrexia) or were conducted in countries where meningococcal infections had been hyper-endemic for several years (e.g. New Zealand) and their results may not be generalizable to the Canadian context.

Despite these limitations, these studies showed that there is a high level of acceptability for meningococcal vaccination among the population and health professionals. Perceiving to be at risk of contracting a meningococcal infection, receiving a health professional's recommendation to be vaccinated and viewing the vaccine as safe and effective were factors associated with decisions on receiving meningococcal vaccination among the population. Perceptions linked to the severity of the disease as well as the safety and effectiveness of the meningococcal vaccine were identified as factors that influenced health professionals' intention to recommend this vaccine. Studies on acceptability of vaccination against meningococcus have also highlighted parents' and health professionals' concerns about vaccine safety and the negative influence that these concerns could have on their decisions about vaccination (e.g. fear of side effects and fear multiple injections).<sup>135-137,139,142,143</sup>

### ***Feasibility of Vaccination Against Serogroup B Meningococcus***

Because the vaccine against serogroup B meningococcus may be administered to children aged two months or more, and adolescents, various scenarios for the future implementation of a vaccination program are possible.<sup>144</sup> Potential strategies include introducing the vaccine as part of a universal program, with or without catch-up vaccination, or using a more "opportunistic" approach, whereby a mass immunization campaign or a vaccination targeting the most at-risk population groups (depending on age and region) would only be launched in the event of an epidemic on the basis of predetermined epidemic thresholds. Since the duration of protection after primary vaccination against serogroup B meningococcus is unknown, the need for booster doses must also be established.

**Table 13 - Issues Concerning Serogroup B Meningococcal Vaccine Scenarios**

	<b>Scenario 1: Vaccination of infants at 2, 4, 6 and 12 months</b>	<b>Scenario 2: Vaccination of infants at 3, 5, 7 and 11 months</b>	<b>Scenario 3: Vaccination of children and adolescents in schools</b>	<b>Scenario 4: Vaccination of groups at risk (outbreak response or wait- and-see strategy)</b>
<b>Acceptability by parents</b>	↑ risk of side effects ↑ number of injections during a single visit No increase in the number of vaccination visits	Additional visits required ↓ risk of side effects compared to scenario 1	↑ risk of side effects compared to no-vaccination scenario ↑ number of injections No increase in the number of vaccination visits	Acceptability issues if vaccine is not available for free to everyone
<b>Acceptability by health care professionals/vaccinators</b>	↑ number of injections during the same visit	↑ vaccinators' workload	↑ number of injections during the same visit	Acceptability issues if vaccine is not available for free to everyone
<b>Operationalization</b>	Relatively easy to achieve ↑ duty of vaccinators	Major issues, ↑ human and financial resources, significant burden on health care system	Relatively easy to achieve ↑ duty of vaccinators	More complex operationalization, because decentralized
<b>Costs</b>	↑ compared to the no-vaccination scenario	↑ costs compared to the no-vaccination scenario and scenario 1	↑ compared to the no-vaccination scenario	↑ compared to the other scenarios
<b>Impact</b>	Vaccination coverage similar to that of other vaccines expected	Possible decrease in vaccination coverage of other antigens	Vaccination coverage similar to that of other vaccines expected	Strategy shown less effective than routine vaccination strategy
<b>Equity</b>	Few equity issues	Few equity issues	Few equity issues	Significant equity issues

The introduction of a new routine program during already scheduled vaccination visits (such as during primary vaccination visits or through school-based programs) should not pose major challenges with respect to feasibility. However, it should be

noted that this would involve the administration of several injections during a single vaccination visit and could increase certain side effects post-vaccination. A systematic literature review was conducted by Hyde et al. to assess the impact that introducing new vaccines would have on vaccination and the entire health care system. A total of 130 articles, published up to September 29, 2010, were analyzed and reported primarily on experience in developed countries. The authors observed that the introduction of new vaccines was more efficient when vaccines were introduced into an existing vaccination strategy and administered in combination with vaccines already on the immunization schedule (combination vaccines). The importance of communication and education to ensure the successful introduction of new vaccines was cited. Lastly, the authors noted that introducing new vaccines generally had little or no impact on vaccination coverage of vaccines already on the children's routine schedule and was associated with a reduction in health care costs in developed countries.

The administration of vaccines during a separate visit (at 3, 5, 7 and 11 or 17 months) could be considered as a possible vaccination strategy. This scenario would have the advantage of reducing the potential risk of side effects post-vaccination. However, there are several constraints linked to the addition of visits to vaccination programs for children. These constraints mainly concern operational aspects and costs (human, physical and financial resources). This scenario would add an extra burden on the vaccine providers and may not achieve program objectives in the age group with the highest incidence due to delay in beginning the vaccination series beyond 2 months of age.

Wait-and-see approaches, such as mass immunization campaigns in response to outbreaks, for vaccination are difficult to implement and have been shown to be less efficient and cost-effective than a routine vaccination strategy.<sup>133,145</sup> Additionally, it is more difficult to achieve high vaccination coverage during a mass campaign than in a routine program for young children. Lastly, mass immunization campaigns lead to heavy workloads for professionals at the expense of other prevention activities.<sup>133</sup> However, this approach could have some advantages, for instance in response to an outbreak or hyperendemic situation to disrupt transmission of disease, in the event that the vaccine provides protection for only a short period of time.

## Program Evaluation

The two most important unknowns concerning the 4CMenB vaccine are the effectiveness of this vaccine in preventing not only invasive disease due to serogroup B, but also other strains of *N. meningitidis*, and the safety of the vaccine. Evaluating these unknowns in the Canadian context remains a challenge. Studies thus far have provided novel immunological correlates of protection and have been based on testing methods that are also new and not widely available. The rarity of



the disease necessitates a coordinated, multi-jurisdictional approach in order for evaluative studies to have enough power for the results to be meaningful. Until the vaccine is used in a population, it will be difficult to fully assess the contribution this vaccine will make to reducing, and possibly eliminating, IMD.

As a pre-requisite for the population-wide use of this vaccine in any Canadian jurisdiction, an integrated funded protocol that addresses surveillance, program evaluation and research should be planned. Considerations for the evaluation of vaccine effectiveness, safety and acceptability are outlined in this chapter, including research areas to address current gaps in evidence.

### Evaluating Vaccine Effectiveness (VE)

Calculation of VE may be determined through epidemiological studies including cohort, case-control and screening study designs. VE can also be inferred indirectly through serologic studies. Epidemiological VE studies require the ability to identify cases, ascertain individual vaccination status or population immunization coverage estimates. Serologic studies require the ability to measure immunogenicity and ascertain individual vaccination status. Below are considerations for VE studies related to the 4CMenB vaccine.

#### Case Ascertainment

IMD has been nationally reportable in Canada since 1924, with national enhanced surveillance introduced in 1992. Enhanced surveillance was established to capture bacteriologic information on IMD cases for the purpose of describing annual trends, and serogroup trends in particular. IMD surveillance is based on a passive, lab-based system. In Canada, IMD is legally notifiable and cases meeting the provincial case definition are reported to provincial/territorial (PT) health authorities.<sup>22</sup> Laboratory-based surveillance identifying *N. meningitidis* is carried out at hospital laboratories or provincial public health laboratories, and all isolates are sent for further characterization to the National Microbiology Laboratory (NML) in Winnipeg. The Agency requests non-nominal, line listed case records from the P/Ts on an annual basis as a component of the Enhanced IMD Surveillance System (eIMD). Frequently, laboratory and epidemiologic (lab-epi) data are not linked and probabilistic matching must be performed retrospectively in order to provide complete data for the eIMD database. NACI recommends that the results of molecular biological investigation of the meningococcus isolates that are sent to NML be included in IMD surveillance reports. Specifically, microbiological analysis describing changes in serogroup, clonal complexes, surface-protein characteristics before and after vaccine implementation.

The capacity to examine traditional microbiologic characteristics of meningococci as well as determine expression of NHBA, NadA, and fHBP antigens of all meningococcal isolates to examine vaccine strain coverage would be beneficial in Canada.<sup>71,148</sup> The Meningococcal Antigen Typing System (MATS) is the only existing test available to obtain this information, and is currently not available for use in Canada as the technology has not been transferred to the NML.

In addition to the national surveillance program described above, active, case-based surveillance for hospital admissions related to laboratory confirmed invasive infection with *N. meningitidis* has been conducted at 12 Immunization Monitoring Program ACTive (IMPACT) pediatric tertiary care centers and surrounding hospitals since 2002. Each IMPACT center has a defined catchment area for which they identify all cases in adults and children admitted at hospitals within this area in order to calculate the annual IMD incidence rate among children and adults in Canada. IMD is not currently one of the vaccine preventable disease targets funded by the Agency; therefore, data collected through this system is not shared at the national level.

At the individual level, not every case of IMD serogroup B in an immunized child is necessarily a vaccine failure. That is if the specific strain did not express the antigens targeted by the vaccine, there would be no expectation of protection. Conversely, if a recipient of the vaccine develops IMD due to another serogroup, and this strain expresses the target antigens, this may indeed constitute a vaccine failure. Defining 4CMenB vaccine failure would be prudent to adequately assess the effectiveness of this vaccine both at the individual and population level.<sup>149</sup>

#### **Ascertaining Vaccination Status**

For both epidemiologic and serologic studies, it is important to know the vaccination status of cases. This information may be gathered through the communicable disease reporting system (a component of the case report form and collected with other case details), or linked to an electronic immunization record.

#### **Ascertaining Population Immunization Coverage**

Immunization registries are the optimal way of capturing accurate timely immunization coverage data. Registries provide a means of assessing uptake of vaccine, acceptability and vaccine effectiveness. Measuring vaccine effectiveness via the screening method would require a wide-scale, population-based program. NACI recommends universal immunization registries in all Canadian provinces to monitor vaccine coverage.

At the National level, the Agency routinely monitors immunization coverage through the Childhood National Immunization Coverage Survey (cNICS). The cNICS is conducted approximately every two years to estimate national vaccine coverage for all routine childhood immunizations recommended for use in Canada. Additional questions on parental knowledge, attitudes and behaviours (KAB) towards immunization are also included to assess factors that influence vaccine coverage, immunization practices and missed opportunities for immunization. The cNICS assesses immunization coverage at four different ages: 2 years, 7 years, 12-14 years, and 17 years.

Fieldwork for the 2013 cycle of the cNICS will begin in September 2013. For the 2013 cycle, the sample size will be expanded to include 43 000 respondents such that it will be possible to estimate immunization coverage at the provincial and

territorial levels for every age group. Data for the 2013 cNICS are expected to be available in mid-2015. In the past, given the modest sample size, only national estimates could be obtained from the cNICS. It is anticipated with the expansion of the survey, the 2013 survey will provide provincial level information. The cNICS is typically used to assess coverage for publicly-funded programs in Canada. If there is no publicly funded program in place for meningococcal B vaccine, it may be difficult to assess coverage in the population based on this survey data. Doses distributed data may be available from the manufacturer.

### Evaluating Vaccine Safety

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) collects data nationally of adverse events and suspected adverse events following immunization, based on voluntary submission reporting by all P/Ts. Within jurisdictions, reporting to public health is voluntary except in Ontario, Saskatchewan, Nova Scotia, Québec, Manitoba, New Brunswick and Northwest Territories, which have mandatory reporting requirements.

The National Immunization Strategy (2003) recommended all federal, provincial and territorial (FPT) immunization programs should have a comprehensive, uniform and compatible approach to immunization safety that includes consideration of surveillance, research, communication and crisis management.<sup>150</sup> Related to the introduction of a new vaccine, a vaccine safety-monitoring plan should be developed, ensuring consideration for enhancements, such as tracking targeted anticipated events following immunization for specific cohorts. NACI recommends enhanced adverse event surveillance such as that of the New Zealand “Intensive Vaccine Monitoring Program” that was used to monitor the safety of NZ-OMV.<sup>151</sup> The feasibility and capacity of jurisdictions to implement such an intensive program will need to be considered.

Ensuring the availability of baseline data regarding anticipated adverse events will assist in the understanding of expected rates of adverse event following immunization, and an increase in those events that may be attributed to the vaccine. Two anticipated issues based on pre-approval studies include day 0-1 fevers with potential for febrile seizures in children aged <2yrs, and Kawasaki syndrome.

Specific to Kawasaki Syndrome, it will be important, at least nationally if not internationally, to develop a mutually agreed upon definition to determine baseline rates of the incidence of this syndrome. The feasibility of developing a Brighton definition to guide causality assessment related to reports of Kawasaki Syndrome as an adverse event following immunization may need to be further explored. The PHAC – CIHR Influenza Research Network (PCIRN) immunization safety assessment network has recently been initiated in various sites across Canada. This network could be engaged for assistance in signal investigation and assistance with causality assessment.

## Evaluating Program Acceptability

Immunization program evaluation includes the acceptability by both health professionals who are responsible for delivering the vaccine, and the public for whom the vaccine is intended. Evaluating the acceptability of the introduction of a new vaccine may include surveys on knowledge, attitudes and beliefs prior to program implementation to ensure educational or training programs on the use of the vaccine are meeting the needs of the target audience. Post-implementation studies may include tracking the impact of the introduction of a new vaccine on other routine immunizations. Specific to the 4CMenB vaccine, research is needed to explore the tolerance of both providers and recipients of the vaccine of the risk associated with the adverse event profile of this vaccine. Also, adherence to recommendations, including the use of antipyretics prior to immunization to reduce fever should be monitored.

## Additional Research Questions

### *Indirect and/or Herd Effects of Immunization*

It will be important to study the impact of immunization using the 4CMenB vaccine on disease incidence in both unvaccinated and vaccinated cohorts. Experience with other vaccines to prevent bacterial diseases, such as the protein-based pneumococcal and meningococcal vaccines, have demonstrated indirect effects such as the reduction of nasopharyngeal carriage, and reduced incidence of disease in cohorts who are not directly protected by the vaccine. Studies of nasopharyngeal carriage of meningococci prior to and after vaccine implementation should be considered by any jurisdiction that plans to implement a population-based program, at the regional or provincial level. Carriage studies should also examine replacement of serogroup as the possible result of immunization programs that effectively reduce carriage for one serogroup, creating a niche for others.

In addition to carriage studies, consideration should be given to conducting sero-epidemiologic studies of both vaccinated and unvaccinated individuals. As there is limited evidence available on the duration of immunity afforded by the 4CMenB vaccine, studies of those who have received vaccine should include investigation of waning immunity.

### *Studies Involving High-risk Groups*

Recommended use of 4CMenB vaccine should be considered for groups at high risk of IMD; however, there is limited evidence on the risk in these groups to serogroup B, and the level of protection that may be provided by the vaccine. Studies are required to examine the immunogenicity in individuals with high risk.

Enhanced surveillance of vaccine failures in high risk groups would be extremely beneficial in terms of understanding risk, duration of protection and informing future vaccine recommendations for high risk groups.

### Unintended Consequences

The introduction of a new vaccine may result in outcomes that are unanticipated or unintended. Vigilance is required. Administrative data may be used to monitor unintended consequences of the use of the 4CMenB vaccine, including an increased burden on the health care system in terms of increased visits to emergency rooms and/or physician visits related to reports of fever or additional immunization visits.

### Modeling/Health Economics

Pre-implementation economic analysis has used a number of assumptions to inform the models, notably vaccine effectiveness, which is based on *in vitro* analysis using the MATS, and the cost of the vaccine. If there is programmatic use of the vaccine, post implementation evaluation will be required to determine how close to the 'real thing' the models have been to inform social and economic cost benefit analysis of the 4CMenB vaccine.

### Surveillance

As discussed above, Canada has both a passive reporting system for the surveillance of IMD, as well as a sentinel system through IMPACT. As more detailed, timely data is reported through IMPACT, it will be important to document the representativeness of the IMPACT data in estimating the burden of meningococcal disease in Canada. Further examination of the data captured through this system, its representativeness and the contribution of this data to provincial, territorial and national reporting is recommended.

## Other Considerations

### Ethical Considerations

Ethical issues of a vaccination program against serogroup B meningococcus must be assessed against the vaccination strategy selected, since the issues will vary accordingly. If a vaccine were to be approved and no programs were in place, only individuals who could afford to buy the vaccine would get vaccinated, meaning that the vaccine would not be accessible to those less affluent. An ethical problem would also arise insofar as, in the presence of a safe and effective vaccine and in the absence of a program, the continuing occurrence of preventable cases of meningococcal infections could be expected. Moreover, if a vaccination strategy targeting only at-risk groups was chosen, equity issues would also be raised.

It is worth noting that public trust is critical to the success of vaccination programs and must be diligently protected.<sup>146,147</sup> It is therefore essential to adequately inform parents about the benefits and risks associated with vaccination so that they can make an informed decision.<sup>146</sup> This is particularly important in the context of vaccination against serogroup B meningococcus because these infections are highly feared by most parents. To respect the principle of the common good, appropriate measures should also be taken to ensure that side effects associated with the serogroup B meningococcal vaccine are minimized to the fullest extent possible,

particularly by avoiding co-administration with other reactogenic vaccines or by recommending the use of antipyretics. Lastly, a publicly funded vaccination against serogroup B meningococcus program may raise issues with respect to the principle of utility (cost-effectiveness). To conclude, it is important to maintain high standards for VE and safety, demonstrate transparency with respect to the rationale underlying the introduction of a new vaccination program and recognize the ethical implications of these decisions.

### Equity Considerations

When making decisions related to prioritization of new immunization programs, PTs may be faced with funding restrictions. In such instances, PTs will have to carefully weigh the costs and benefits of each, and to consider other options to facilitate availability of vaccine if it is not publicly funded.

### Political Considerations

The authority of the allocation of resources for vaccines may rest with various levels of government, and thus be outside of the control of provincial and territorial immunization program decision makers.

## Recommendations

In developing the recommendations, NACI and MBPPTG considered the burden of illness from IMD, the safety and immunogenicity of the newly authorized 4CMenB vaccine, as well as other aspects of overall immunization strategies. MBPPTG further considered social and economic cost benefits, acceptability, feasibility, equity, ethical, and political considerations.

Recommendations of NACI and MBPPTG for the use of the multicomponent meningococcal B vaccine in Canada are limited by the lack of evidence and the range of uncertainty of the underlying assumptions, particularly those concerning the vaccine's coverage of circulating strains, herd immunity, effectiveness and potential adverse effects of vaccination at the population level. These recommendations will be updated at the time new data becomes available.

### Recommendation 1:

**Multi-component meningococcal serogroup B (4CMenB) vaccine may be considered on an individual basis, for persons greater than or equal to two months of age, to protect against invasive meningococcal disease caused by relevant strains of serogroup B *Neisseria meningitidis*. (NACI Recommendation Grade B)**

For the individual, there is sufficient preliminary evidence that 4CMenB vaccine is immunogenic, and may offer protection against strains expressing antigens covered by the vaccine, when given according to the schedules used in clinical trials. It has an acceptable safety profile with variable rates of adverse effects, as outlined above.



In Canada, 4CMenB vaccine has been authorized for use in individuals from two months through 17 years of age. However, data reported in clinical trials indicates that 4CMenB vaccine is immunogenic and safe when given to adults up to 55 years of age using a two dose schedule with an interval of at least one month between doses. When advising on immunization with 4CMenB vaccine, individual preferences, regional serogroup B IMD incidence and strain susceptibility based on MATS testing should be considered. In circumstances in which the potential benefits of 4CMenB vaccine appear to outweigh the risks of adverse events following immunization, the use of 4CMenB vaccine should be considered. When giving the vaccine, vaccine recipients or parents/caregivers should be informed about anticipated local and systemic reactions and provided instructions for their optimal management. Common adverse events include pain and fever.

### **Recommendation 2:**

**There is insufficient evidence for the use of multi-component meningococcal serogroup B (4CMenB) vaccine in routine immunization programs for Canadian infants, children, adolescents and adults. (NACI recommendation Grade I)**

Serogroup B is the most common IMD causing strain in Canada. From 2007 to 2011, on average there were 22 cases of meningococcal B IMD reported in Canada in children less than one year of age and 21 cases in children one to four years of age. The majority of serogroup B cases have occurred in one province in children under four years of age.

There are no available effectiveness studies at the population level for this vaccine, and the only evaluation of strain susceptibility (i.e. strain characterization) in Canada comes from a single IMPACT study that used the MATS assay, whose validity in the field has not yet been assessed. Based on the MATS assay, 66% of the overall proportion of Canadian serogroup B meningococcal strains is predicted to be susceptible to the 4CMenB vaccine. Given this information and the fact that cases occur too early in life to be vaccine preventable, an infant vaccination in Canada that is 100% effective, with 100% population coverage and that protects until age four years would theoretically, prevent up to 11 cases in infants under one year of age and 16 cases in children from one to four years of age. A total of up to two deaths per year would be prevented in these age groups.

The risks of introducing the vaccine to the Canadian population as a whole remain unknown. There are concerns about high rates of fever reported in clinical trials (particularly when administered to infants simultaneously with other recommended vaccines) and other observed adverse events (i.e. febrile seizures, arthralgia, Kawasaki Disease) that may translate to high frequencies of adverse events should this vaccine be used widely in the general population.



On a population level, there is insufficient evidence to support the use of 4CMenB vaccine in routine immunization programs in Canada given the following: currently available information on burden of disease; predicted level of strain susceptibility and vaccine safety; uncertainty regarding the duration of protection; and the lack of data on the effects of 4CMenB vaccine on meningococcal carriage as well as its impact on herd immunity. However, in circumstances in which the potential benefits of 4CMenB vaccine may outweigh the uncertainty of using the 4CMenB vaccine at the population level, regional serogroup B IMD incidence and strain susceptibility based on MATS testing should be considered as part of decision making.

A detailed discussion of all outlined considerations is presented in the [Vaccine Characteristics](#) section of this document.

### **Recommendation 3:**

**Multi-component meningococcal serogroup B (4CMenB) vaccine should be considered for active immunization of individuals greater than or equal to two months of age who are at high risk of meningococcal disease to prevent invasive meningococcal disease caused by serogroup B *N. meningitidis*. (NACI Recommendation Grade I)**

NACI identifies the following groups as being at higher risk of meningococcal disease than the general population:

1. Individuals with specific underlying medical conditions:
  - persons with anatomic or functional asplenia (including sickle cell disease)
  - persons with congenital complement, properdin, factor D or primary antibody deficiencies
  - persons with acquired complement deficiencies (e.g. those receiving eculizumab)

NACI has previously stated that meningococcal vaccines could be considered for individuals with HIV.<sup>86</sup>

2. Individuals who are at an ongoing risk of exposure:
  - research, industrial and clinical laboratory personnel who are routinely exposed to *N. meningitidis*
  - military personnel during recruit training (military personnel may be at increased risk when accommodated in close quarters)
  - see [Recommendation 8](#) below regarding travellers

This recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion. NACI was unable to provide a stronger recommendation due to insufficient evidence regarding the safety and immunogenicity of 4CMenB vaccine in individuals at higher risk of IMD. 4CMenB vaccine has only been studied in a small number of laboratory workers but not in any of the other high risk groups mentioned above.

#### **Recommendation 4:**

**Multi-component meningococcal serogroup B (4CMenB) vaccine should be considered, in addition to chemoprophylaxis, for protection of individuals 2 months of age or older having close contact with a case of invasive meningococcal disease caused by serogroup B *N. meningitidis*. (NACI Recommendation Grade I)**

Close contacts of individuals with meningococcal infections have an increased risk of developing IMD and should receive vaccination (immunoprophylaxis) in addition to chemoprophylaxis. This risk is greatest for household contacts and may persist for up to 1 year after disease in the index case. Vaccination of close contacts of a case of serogroup B IMD should be carried out independent of MATS assay result or other tests of strain susceptibility to the vaccine to ensure there are no delays in contact management. The following individuals should be considered for immunoprophylaxis:

- Household contacts of a case of IMD,
- Persons who share sleeping arrangements with a case of IMD,
- Persons who have direct nose or mouth contamination with oral or nasal secretions of a case of IMD (e.g. kissing on the mouth, shared cigarettes, shared drinking bottles),
- Children and staff in contact with a case of IMD in child care or nursery school facilities.

This recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion. NACI was unable to provide a stronger recommendation due to insufficient evidence regarding the effectiveness of 4CMenB vaccine.

#### **Recommendation 5:**

**During invasive meningococcal disease outbreaks caused by serogroup B *N. meningitidis* or the emergence of hyperendemic and/or hypervirulent *N. meningitidis* strains that are predicted to be susceptible to the vaccine based on MATS testing, immunization with the multi-component meningococcal serogroup B (4CMenB) vaccine is recommended for individuals greater than or equal to two months of age. (NACI Recommendation Grade I)**

Previous widespread use of conjugate serogroup C and serogroup B OMV vaccines against emerging hyperendemic and/or hypervirulent strains expressing homologous antigens as those present in a vaccine has been demonstrated to be an effective public health strategy for managing clonal IMD outbreaks. This recommendation is consistent with the public health management approach taken for other meningococcal serogroups, in Canada and internationally, and is recommended on the basis of expert opinion.

Consultation with public health officials and/or experts in communicable disease is required for optimal management of meningococcal disease outbreaks.

#### **Recommendation 6:**

**Routine prophylactic administration of acetaminophen and/or separating 4CMenB vaccination from routine vaccination schedule may be considered for preventing fever in infants and children up to three years of age. (NACI Recommendation Grade I)**

As high rates of fever observed in the clinical trials represent an important adverse event, different strategies for reducing this risk should be considered in discussions with vaccine recipients and caregivers. High rates of fever have been reported in the first four days (up to 63% of children under 12 months of age and 48% of children 12-24 months of age) when the vaccine was administered concomitantly with routine infant vaccines. Preliminary safety data have demonstrated that the use of acetaminophen immediately prior to and following vaccination can reduce fever rates up to 50% after the first dose without altering the immunogenicity of the vaccine; however, while it may be presumed that fewer fevers should lead to fewer febrile convulsions, there is no evidence that prophylactic use of acetaminophen prevents febrile seizures in children. Prophylactic use of acetaminophen is not recommended for other vaccines. The effect of ibuprofen on fever and immunogenicity of 4CMenB vaccine has not been evaluated.

#### **Recommendation 7:**

**It is recommended that a comprehensive surveillance and vaccine evaluation program be implemented to monitor and evaluate the effects of immunization with the 4CMenB vaccine, whether for routine use, outbreaks or for high-risk groups/settings. (NACI Recommendation Grade A)**

4CMenB vaccine is novel and uncertainty remains with respect to both potential benefits and potential risks of population-wide immunization. Although pre-marketing studies to date have not demonstrated an increased risk of many clinically serious significant adverse events, they were of relatively small sample size and short duration of follow-up (maximum length of follow-up to-date is 39 months following initial vaccination with 4CMenB vaccine at 2 months of age). Similarly, there are currently no data on the efficacy and effectiveness of the 4CMenB vaccine, particularly its potential to protect against Canadian

meningococcal strains. Consequently, it will be important to conduct effectiveness and post-marketing safety studies following the introduction of the 4CMenB vaccine in Canada (i.e. monitoring for increased rates of KD and febrile seizures).

Validation of the MATS assay, comprehensive microbiological and enhanced epidemiological surveillance, and other program related issues including the potential effects of systematic prophylactic use of acetaminophen, the impact of 4CMenB vaccination on coverage of other routine infant immunization programs, duration of protection following vaccination, effects on herd immunity and carriage, effect on serogroups other than B and the vaccine's impact on the control of outbreaks and population groups that have not been studied in clinical trials require further surveillance, research and evaluation.

#### **Recommendation 8:**

**Travellers do not need to receive 4CMenB vaccine unless they are travelling to an area with a hyperendemic strain or an outbreak that is known to be caused by *N. meningitidis* serotype B that can be prevented by the vaccine. (NACI Recommendation Grade I)**

Data concerning the duration of protection, strain match of the vaccine to circulating strains in different geographic areas and the use of 4CMenB in short or long-term travellers is currently inadequate or lacking. Long-term travellers and those who will be in close contact with the local population through accommodation, public transport, or work are at likely the same risk of IMD as the local population. If the local population is at increased risk due to a hyperendemic strain or an outbreak is occurring that is known to be caused by a *N. meningitidis* serotype that can be prevented by the vaccine, then the traveler should be vaccinated. Since severe adverse reactions to the vaccine are uncommon, and the disease is one that can have a fatal outcome within a very short period, it may be prudent to proceed with vaccination when the traveller is uncertain about the exact nature of their potential exposures to the local population.

## **Overall Recommendation**

### **Who should receive this vaccine?**

Individuals ( $\geq 2$  months of age) immunized under the following circumstances:

- If they are at high risk of meningococcal disease caused by serogroup B *N. meningitidis*.
- If they have been in close contact with a case of IMD caused by serogroup B *N. meningitidis*.

- If they are at risk during IMD outbreaks caused by serogroup B *N. meningitidis* or the emergence of hyperendemic and/or hypervirulent *N. meningitidis* strains that are predicted to be susceptible to the vaccine based on MATS testing.

The 4CMenB vaccine is contraindicated in individuals with a serious allergy to any vaccine component or previous dose.

There are no studies of 4CMenB vaccine in the following populations:

- pregnant or lactating women;
- infants less than 2 months of age;
- individuals over 55 years of age;
- individuals with a chronic medical condition;
- those who have had a previous meningococcal infection.

### Should this vaccine be included in routine immunization schedules?

Currently, it is not recommended to include the multicomponent meningococcal serogroup B (4CMenB) vaccine in routine immunization programs for Canadian infants, children, adolescents and adults.

## Conclusion

The scientific evidence regarding the novel multicomponent meningococcal serogroup B (4CMenB) vaccine Bexsero® has been reviewed in order to provide medical, scientific, and public health advice on the use of the vaccine in the Canadian population.

Given the current available information on the burden of IMD in Canada, as well as the lack of evidence and the range of uncertainty of the underlying assumptions, particularly those concerning the predicted level of strain susceptibility, duration of protection, impact on meningococcal carriage and herd immunity, and potential adverse effects of vaccination at the population level, a recommendation for the implementation of a routine immunization program for meningococcal serogroup type B in Canada cannot be made at this time.

Future research and surveillance activities should address the potential of 4CMenB vaccine to protect against Canadian meningococcal B strains and other meningococcal serogroups, as well as address issues around vaccine safety, vaccine efficacy, duration of protection, herd immunity, carriage, special populations and surveillance needs.

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