Statement on the Multicomponent Meningococcal B (4CMenB) Vaccine

Provincial Infectious Diseases Advisory Committee (PIDAC)

October 2014
Public Health Ontario

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The Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I) is a multidisciplinary scientific advisory body that provides evidence-based advice to the Ontario Agency for Health Protection and Promotion (Public Health Ontario) matters related to immunization. PIDAC-I provides advice by applying scientific knowledge and the best available evidence to vaccine programs and issues in Ontario, drawing on, but not repeating, the safety and efficacy analyses provided in the Canadian National Advisory Committee on Immunization (NACI) recommendations.

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Introduction

*Neisseria meningitidis* is a rare but serious cause of invasive meningococcal disease (IMD) which can be associated with substantial long-term sequelae and case fatality, in Ontario and worldwide. It is also a disease associated with a high degree of public concern as both individual cases and clusters of cases receive significant media interest, especially if these result in death. Meningococci vary in the immunologic reactivity of the polysaccharide capsule and on that basis can be classified into 12 distinct serogroups. Globally, the most common serogroups are A, B, C, W-135, X and Y. Within Canada, including Ontario, four serogroups (B, C, W-135 and Y) are responsible for the majority of cases of invasive meningococcal disease. There can be further classification into serotypes and serosubtypes.

Many meningococcal serogroups are vaccine-preventable. Ontario has two routine immunization programs addressing IMD, as well as a high risk program. Since September 2004, Ontario has had a single-dose meningococcal C conjugate vaccine (MCCV) program for toddlers at 12 months of age. In January 2005, an MCCV program for Grade 7 students was introduced, and in 2009, this was changed to a quadrivalent meningococcal vaccine (MCV4) program. MCV4 vaccine targets serogroups A, C, Y and W-135. Beyond these routine immunization programs, meningococcal vaccines are also provided through publicly funded programs to select high-risk Ontarians (described further within this document). Until recently, serogroup B was not vaccine-preventable.

On December 5, 2013, Health Canada issued a Notice of Compliance (NOC) for Bexsero® (4CMenB, Novartis Vaccines), a multicomponent meningococcal serogroup B vaccine. The Bexsero® vaccine contains four main components: factor H binding protein (fHbp) variant 1.1, Neisserial Adhesin A (NadA), Neisseria Heparin Binding Antigen (NHBA) and Porin A (PorA) P1.4 as the main antigen of Outer Membrane Vesicles (OMV) derived from *N. meningitidis* serogroup B, strain NZ 98/254. A second serogroup B vaccine is under development by Pfizer.

In June 2012, following a proposal from the National Immunization Strategy Task Group (NIS-TG), a new and time-limited Meningococcal B Pilot Project Task Group (MBPPTG) was created in order to develop guidance for the use of the 4CMenB vaccine, including both scientific and technical advice in addition to program and policy recommendations. The former are traditionally summarized within National Advisory Committee on Immunization (NACI) statements and the latter within recommendations from the Canadian Immunization Committee (CIC). A challenge for vaccine decision-makers among Canadian provinces and territories (P/Ts) has been a significant time delay between a new vaccine’s NOC date, and the issuing of both NACI and CIC guidance to support P/T immunization decision-making and program planning. On March 26, 2014, a common guidance statement addressing the newly approved 4CMenB vaccine was released. The statement contains integrated recommendations (hereafter referred to as the common guidance document).
Objective

The objective of this report is to briefly review the common guidance statement on the use of the 4CMenB vaccine within the context of Ontario’s serogroup B IMD epidemiology, the vaccine’s product monograph, existing Ontario IMD vaccine policy, available cost-effectiveness analyses and other supporting literature, in order to outline options for the Ontario Ministry of Health and Long-Term Care (MOHLTC) to consider with respect to 4CMenB immunization program planning. Duplication of details contained within the common guidance statement have been avoided and the reader is directed to the statement for a comprehensive summary of the vaccine’s immunogenicity, safety, and a detailed review of programmatic considerations.

Epidemiology of serogroup B IMD in Ontario

The epidemiology of IMD, and serogroup B in particular, within Ontario has been examined in detail. The data source for these analyses is a linked dataset from two sources: confirmed IMD cases from Ontario’s reportable diseases database, the integrated Public Health Information System (iPHIS) and laboratory isolates from the Public Health Ontario Laboratory (PHOL), over the period of January 1, 2000, to December 31, 2012. This updates a previous analysis from Ontario.1

Over the last 13 years in Ontario, the annual incidence of IMD (all serogroups) has gradually fallen (Figure 1) with notable serogroup-specific trends (Figure 2). Since 2002, serogroup B has been responsible for the largest proportion of cases of IMD. Over the surveillance period, a total of 299 cases of serogroup B IMD were identified, with annual incidence rates ranging between 0.11 and 0.27 per 100,000 population. The age of cases ranged from 13 days to 101 years with a median age of 18 years, and a slight male predominance (54.0% of cases). The overall case fatality ratio (CFR) was 11.3%, with some variation with age. The CFR among infants under one year of age was 15.3%.

Figure 1. Number of cases and incidence rate per 100,000 of IMD in Ontario, overall and by serogroup B, 2000–12
Figure 2. Annual incidence of IMD in Ontario, by serogroup, 2000–12 (n=689*)

*Notes: 3 serogroup A, 1 serogroup Z, 86 non-groupable and 14 cases with unknown serogroup have been excluded

The annual age-specific incidence for serogroup B IMD in Ontario is shown in Figure 3. The peak incidence occurs in infants under one year of age (3.5 per 100,000 population) with a smaller peak occurring between the ages of 15 to 19 years (0.3 per 100,000). Among the 62 cases that occurred in infants under one year of age between 2000 and 2012, the majority (45/62, 73%) occurred before 6 months of age; 48% occurred before 4 months of age (Figure 4).

Figure 3. Annualized age-specific incidence for serogroup B IMD in Ontario, 2000–12 (n=297*)

*Notes: Excludes two cases with unknown age
Figure 4: Proportion of serogroup B IMD cases in Ontario by age groups, 2000–12 (n=297*)

*Notes: Excludes two cases with unknown age
Licensed indications and schedules

The licensed indication for Bexsero® is for immunization of individuals from 2 months to 17 years of age against invasive disease caused by *N. meningitidis* serogroup B strains. Although clinical trials have included adults ranging from 18 to 50 years of age, the vaccine does not currently have an adult age indication. The recommended schedule varies by age at initiation. The approved schedules are summarized in Table 1.

**Table 1. Summary of approved schedules by age at series initiation**

<table>
<thead>
<tr>
<th>Age at series initiation</th>
<th>Number of doses</th>
<th>Schedule</th>
<th>Need for (further) booster dose(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 5 months</td>
<td>3+1</td>
<td>2, 4 and 6 months of age*</td>
<td>Yes, at 12–23 months of age</td>
</tr>
<tr>
<td>6 to 11 months</td>
<td>3</td>
<td>Interval of 2 months between dose 1 and dose 2. The third dose should be given in second year of life (12–23 months of age) with a minimum of 2 months.</td>
<td>Has not been established</td>
</tr>
<tr>
<td>12 to 23 months</td>
<td>2</td>
<td>Interval of 2 months between dose 1 and dose 2</td>
<td>Has not been established</td>
</tr>
<tr>
<td>2 to 10 years</td>
<td>2</td>
<td>Interval of 2 months between dose 1 and dose 2</td>
<td>Has not been established</td>
</tr>
<tr>
<td>11 to 17 years</td>
<td>2</td>
<td>Interval of 1 month between dose 1 and dose 2</td>
<td>Has not been established</td>
</tr>
</tbody>
</table>

*An alternate schedule for infants 2–5 months of age is to deliver the first three doses at 2, 3, and 4 months of age, although the product monograph indicates the immune response to the NHBA antigen is lower when this schedule is followed.*

4. [Source](#)
Summary of recommendations from the NACI/Meningococcal B Pilot Project Task Group (MBPPTG) Common Guidance Statement on 4CMenB Vaccine

In March 2014, the joint NACI/CIC statement, which contained several recommendations for the use of the 4CMenB vaccine in Canada, was finalized. It is important to note that the statement specifically cautions that the strength of the recommendations of NACI and MBPPTG were limited by a lack of evidence about the performance of the vaccine outside of select clinical trial populations and a range of uncertainty around key issues. These issues include the vaccine’s efficacy in preventing serogroup B IMD among circulating strains, indirect effects (i.e., herd immunity), vaccine effectiveness and safety. The eight key recommendations and their corresponding evidence grade are reproduced here:

1. 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)

2. There is insufficient evidence for the use of 4CMenB vaccine in routine immunization programs for Canadian infants, children, adolescents and adults. (NACI recommendation Grade I)

3. 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)

4. 4CMenB vaccine should be considered, in addition to chemoprophylaxis, for protection of individuals two 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)

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 Meningococcal Antigen Typing System (MATS) testing, immunization with the 4CMenB vaccine is recommended for individuals greater than or equal to two months of age. (NACI Recommendation Grade I)

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)

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)
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)

The remainder of this document will focus on discussing recommendations numbers 2–4 and 7 within the Ontario context, as these recommendations pertain to immunization program planning and disease surveillance. Recommendations for individual client use (i.e., counselling with a specific clinician–client encounter) and for pre-travel immunization are considered out of scope for this document. The use of vaccine for outbreak management in Ontario would occur through existing mechanisms including Ontario Outbreak Investigation Coordination Committee (OOICC) teleconferences and the provision of expert scientific and medical opinion from Public Health Ontario and other experts as appropriate, depending on the epidemiology of the outbreak.

During the review, the complexity of the process and eventual decision-making surrounding the vaccine was noted. Serogroup B IMD is rare but associated with a high degree of public dread. It disproportionately affects infants and young children and can result in death or disability. However, there are many unknowns associated with the 4CMenB vaccine, the first vaccine developed through the process of reverse vaccinology. These include how well immunogenicity and strain coverage, as assessed using the MATS assay, correlate with protection; its impact on nasopharyngeal carriage and subsequently herd effects; and, as with any new vaccine, duration of protection and vaccine safety. These scientific unknowns combined with unfavourable cost-effectiveness estimates, even with varying disease incidence, vaccine price, discounting and other parameters, have led PIDAC-I to support the recommendations made by NACI and the MBPPTG. These issues are summarized within the common guidance document.

**Cost-effectiveness analyses**

Four studies have examined the cost-effectiveness of introducing the 4CMenB vaccine into routine immunization programs. Two studies contain Canadian data: an Ontario model\(^7\)\(^8\) and a model funded by the vaccine manufacturer, Novartis.\(^5\) Two international studies, from the Netherlands\(^9\) and the United Kingdom (UK)\(^10\) are also available, although disease incidence and health care costs vary by country, so generalization to the Canadian context should be made with caution. Each model varies in important features including disease burden, strain coverage, discounting, and the programs modelled. Importantly, the studies also differ in whether they explicitly model herd immunity effects, which is a core feature of dynamic models. The common guidance statement provides a comprehensive overview of these studies, including definitions of concepts used in health economic evaluations and a discussion of the theoretical and interpretive issues related to modelling within health economic evaluations. A comprehensive summary table which compares and contrasts the four studies in detail is also available within the document.

In brief, no published studies have found the introduction of a routine 4CMenB vaccination program to be cost-effective under commonly used cost-effectiveness thresholds. However, the model developed for the UK has been revised since its original publication\(^10\) and has led the UK’s Joint Committee on Vaccination and Immunisation to recommend implementation of a routine infant program on the basis of favourable cost-effectiveness thresholds at an (unpublished) vaccine price that is below the current list price for the vaccine.\(^11\) While most decision-makers do not use an explicit threshold, $50,000 per quality-adjusted life year (QALY) is often used to indicate value for money.\(^12\) The incremental cost-effectiveness ratio (ICER) for a routine 4CMenB infant immunization program (four doses, no catch-up) ranged from C$238,000 per QALY in the dynamic Novartis model\(^5\) when examined using the societal perspective (personal communication, Dr. Natasha Crowcroft, July 13, 2014) to C$5.6 million per QALY in the static Ontario model using the health care payer perspective.
ICERs for a UK program ranged from €91,800 per QALY (dynamic) to €162,800 per QALY (static) from a health care payer perspective in the published analysis although as noted above, the UK model has been revised following advice from JCVI; the revised model has not been published and the JCVI statement does not outline the modified ICER values. The Dutch study reported an ICER €244,000 per QALY from a societal perspective using a static model. Of note, the disease incidence of serogroup B IMD in the UK and the Netherlands are eight and six times higher than in Ontario, respectively, which challenges the generalization of these models to the Ontario context. A brief outline of the four studies is available in Table 2, with ICERs converted from the relevant currency and then inflated to 2013 Canadian Dollars.

The Ontario analysis uses a Markov model to characterize the natural history of serogroup B IMD for a hypothetical Ontario birth cohort of 150,000 infants followed over their full lifespan. A routine infant immunization program using four doses is compared to no immunization. The key parameters used in the base case analysis included the following: vaccine efficacy was assumed to start after completing the second dose of vaccine at four months, 90% vaccine effectiveness, 66% strain coverage, 97% vaccine coverage, 10-year duration of protection, and a vaccine cost of C$90 per dose. Administration costs, costs associated with public health management of contact and outbreak management, and Ontario health care costs for the treatment of cases and adverse events following immunization (AEFIs) were all included in the model. Costs and QALYs were discounted at 5% (but also presented undiscounted and discounted at 3%). Disease transmission dynamics (i.e., herd effects) were not explicitly modelled although they were approximated in a scenario analysis, which assumed that all cases due to the strains covered by the vaccine would be prevented. This is an extremely optimistic assumption of vaccine indirect effects.

Using the parameters above, the Ontario model estimated that vaccinating a cohort of 150,000 infants would prevent 4.6 cases of serogroup B IMD and 0.5 related deaths over the lifetime of the cohort, equivalent to 13.16 discounted (52.15 undiscounted) QALYs gained at a price of more than C$55.3 million. The ICER of the program was estimated to be C$4.2 million per QALY gained discounted (C$1.05 million per QALY gained undiscounted). ICERs remained above commonly used thresholds even after increasing disease incidence tenfold (C$414,495 per QALY gained, discounted), at a vaccine price of C$0 (C$94,106 per QALY gained, undiscounted) and if including broad herd effects (C$2.2 million per QALY gained, discounted; C$430,340 per QALY gained undiscounted). If varying both disease incidence and vaccine cost, the vaccine program became economically attractive (C$50,000 per QALY) if serogroup B IMD incidence was at least 3.3 times the current incidence and the vaccine price was less than C$10 per dose (discounted analysis).

Details for the Novartis-developed model are taken from the common guidance document. The MBPPTG obtained written information on the model from Novartis for inclusion within the document as the model has not yet been published. It used Canadian-specific data and predicted outcomes within a dynamic model using both societal and health care payer perspectives. The ICER estimate from the Novartis model for a routine infant program (four doses) was C$730,000 per QALY from a health care payer perspective. When modelling a concurrent infant and adolescent program the ICER was reduced to C$416,000 per QALY when examined from a health care payer perspective and C$311,000 per QALY when assessed from a societal perspective. The common guidance statement notes that the cost of vaccine would have to be reduced to C$20 or less in order to generate ICERs less than C$100,000 per QALY, for the concurrent infant and adolescent program even while adopting the more economically favourable societal perspective. The published UK model found that the vaccine price would need to be about £9 per dose for any of the routine infant strategies modelled to be cost-effective at the threshold used in the UK (< £30,000 per QALY). The model from the Netherlands found that routine infant vaccination would only be cost-effective using a threshold of €20,000 per QALY with a vaccine priced well below €10 per dose.

Common critiques of the modelling work undertaken to date include whether herd immunity was accounted for, whether cross-protection against other serogroups was assumed, and choice of discount rates. As
previously outlined, the models differ with regard to their assumptions for herd immunity. Other vaccines, e.g., targeting *Haemophilus influenzae* type b (Hib), pneumococcal and serogroup C IMD, all of which are conjugate vaccines, have demonstrated an impact on nasopharyngeal carriage and consequently, herd immunity. One randomized clinical trial has examined the impact of 4CMenB vaccine on nasopharyngeal carriage among university students in the UK. Primary analyses did not reveal a significant impact of the vaccine on carriage, although a modest reduction in carriage across all serogroups was found in the secondary analyses. To definitively establish whether Bexsero® has an impact on carriage will require large-scale carriage studies. There is also discussion about whether the vaccine will provide cross-protection against other serogroups, as the vaccine contains multiple antigens which are likely to be present as subcapsular proteins in a proportion of isolates from other serogroups. The extent to which there is significant cross-protection is an area of study in ongoing clinical trials and has been identified within the common guidance document as a research priority. Finally, the choice of discount rates (i.e., the discount rate applied to future costs and benefits) has an impact on cost-effectiveness because immunization programs, by their nature, accrue costs in the present to prevent future costs related to health service utilization, and realize future benefits through the prevention of death and disability. The Ontario model used a discount rate of 5% for both costs and health outcomes, as recommended by Canadian and other guidelines. The Novartis-funded model used a discount rate of 3.0–3.5% for costs and 1.5–3.0% for health outcomes, with further variability used within the Dutch and UK models. In all the models, changes in discount rates were explored in sensitivity analyses; in no study did a change in the discount rate alone result in an ICER reaching commonly used cost-effectiveness thresholds. All models found that disease incidence and vaccine price were more influential drivers of cost-effectiveness. The changes made to the UK model which informed the JCVI recommendation for a routine infant program included additional quality of life losses associated with the short term phase of IMD and quality of life losses to family members; new data on minor and severe sequelae following IMD; an increased incidence of IMD; and a proportion of litigation costs associated with meningococcal disease in the UK’s National Health Service.

Finally, no cost-effectiveness studies were found in the published literature, nor referred to within the common guidance statement, regarding the use of 4CMenB vaccine for contact or outbreak management, nor for primary prevention among individuals with medical conditions that place them at higher risk of IMD. This is not surprising as health economic assessments for vaccine use in these scenarios tend to be conducted infrequently.
<table>
<thead>
<tr>
<th>Model source country</th>
<th>Dynamic or static</th>
<th>Perspective</th>
<th>Program modeled</th>
<th>Discounted incremental cost-effectiveness ratios (ICERs): cost per quality-adjusted life year (QALY) in base case analysis</th>
<th>Conversion of discounted ICERs into 2013 Canadian dollars²</th>
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<tbody>
<tr>
<td>Netherlands</td>
<td>Static</td>
<td>Societal</td>
<td>Routine infant program (4 doses)</td>
<td>€244,000 per QALY</td>
<td>C$402,220 per QALY</td>
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<td></td>
<td></td>
<td></td>
<td>Routine infant program (4 doses) + booster at 12 years</td>
<td>€247,000 per QALY</td>
<td>C$407,166 per QALY</td>
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<td>UK</td>
<td>Static</td>
<td>Health care payer</td>
<td>Routine infant program (4 doses)</td>
<td>£162,800 to 164,100 per QALY, depending on schedule</td>
<td>C$341,177 to 343,902 per QALY, depending on schedule</td>
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<tr>
<td></td>
<td>Static</td>
<td></td>
<td>Routine infant program (4 doses) with catch-up in 1-17 year olds</td>
<td>£290,000 per QALY</td>
<td>C$607,748 per QALY</td>
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<td>Dynamic</td>
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<td>Routine infant program (4 doses)</td>
<td>£91,800 to 96,000 per QALY, depending on schedule</td>
<td>C$192,384 to 201,185 per QALY, depending on schedule</td>
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<td>Dynamic</td>
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<td>Routine infant program (4 doses) with catch up in 1- to 4-year-olds (3 doses) and 5- to 17-year-olds (2 doses)</td>
<td>£83,400 per QALY</td>
<td>C$174,780 per QALY</td>
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<td>Ontario</td>
<td>Static</td>
<td>Health care payer</td>
<td>Routine infant program (4 doses)</td>
<td>C$5,589,000 per QALY</td>
<td>C$5,579,499 per QALY</td>
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<tr>
<td>Canada</td>
<td>Dynamic</td>
<td>Health care payer</td>
<td>Routine infant program (4 doses)</td>
<td>C$730,000 per QALY</td>
<td>C$728,759 per QALY</td>
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<tr>
<td></td>
<td></td>
<td>Societal</td>
<td>Routine infant program (4 doses)</td>
<td>C$238,000 per QALY¹</td>
<td>C$237,595 per QALY</td>
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<tr>
<td>Model source country</td>
<td>Dynamic or static</td>
<td>Perspective</td>
<td>Program modeled</td>
<td>Discounted incremental cost-effectiveness ratios (ICERs): cost per quality-adjusted life year (QALY) in base case analysis</td>
<td>Conversion of discounted ICERs into 2013 Canadian dollars(^2)</td>
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<tr>
<td>Health care Payer</td>
<td>Dynamic</td>
<td>Routine infant program (4 doses) and adolescent program (2 then 1 dose)</td>
<td>C$416,000 per QALY</td>
<td>C$415,293 per QALY</td>
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<tr>
<td>Societal</td>
<td>Static</td>
<td>Routine infant program (4 doses) and adolescent program (2 then 1 dose)</td>
<td>C$311,000 per QALY</td>
<td>C$310,471 per QALY</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
1. Personal communication, Dr. Natasha Crowcroft, July 13, 2014.
2. The monetary unit used by the Netherlands model was 2009 Euros and the monetary unit used by the UK model was 2008 British Pounds (GBP). As per the relevant published Bank of Canada rates, one Canadian Dollar is equivalent to 1.59 (2009) Euros. One Canadian Dollar is equivalent to 1.96 (2008) GBP. Following currency conversion, cost estimates were inflated to 2013 Canadian Dollars using the health care component of the Consumer Price Index (CPI). Both the Novartis model and the model by Tu et al., used 2012 Canadian Dollars as the monetary unit in their original analyses. These estimates have also been adjusted to 2013 Canadian Dollars using the CPI.
Use of prophylactic acetaminophen at the time of 4CMenB vaccination

NACI and the MBPPTG recommend that routine prophylactic administration of acetaminophen (and/or separating 4CMenB vaccination from the routine vaccination schedule) “may be considered” for preventing fever in infants and children younger than three years of age. The rationale for this is the relatively high rates of fever observed in clinical trials. The common guidance document notes that in the first four days following vaccination in clinical trials, fever was noted in up to 63% of children under 12 months and up to 48% of children 12 to 24 months of age when the vaccine was administered concomitantly with routine infant vaccine. Clinical trial data have also shown that prophylactic use of acetaminophen immediately prior to and following vaccination can reduce fever rates up to 50%, with no detrimental impact on immunogenicity. The impact of prophylactic ibuprofen on 4CMenB vaccine immunogenicity and fever has not been assessed. The reader is directed to the common guidance statement for further details on the safety and immunogenicity of the vaccine.
4CMenB Vaccine for use among individuals with high-risk medical conditions

In its previous advice, NACI identified a number of groups as being at higher risk of IMD relative to the general population. This includes individuals in particular occupations, including laboratory workers who may be routinely exposed to *N. meningitidis*, military recruits, certain travelers, and individuals with the following medical conditions:

- Anatomic or functional asplenia (including sickle cell disease)
- Congenital complement, properdin, factor D or primary antibody deficiencies
- Acquired complement deficiencies (i.e., those receiving the treatment eculizumab)
- HIV infection

The Ontario immunization schedule provides public funding of the quadrivalent meningococcal conjugate vaccine (MCV4) to individuals at high risk of IMD. Ontario also funds polysaccharide vaccine for high-risk individuals who are older than the age indication of licensed MCV4 products. At present, individuals with the following medical conditions are eligible to receive publicly funded MCV4 vaccine in the province:

- Anatomic or functional asplenia (including sickle cell disease)
- Congenital complement, properdin, factor D or primary antibody deficiencies
- Cochlear implant recipients

Of note, individuals with acquired complement deficiency secondary to receipt of treatment with the biologic agent eculizumab (Soliris™) and those with HIV infection are not currently eligible for publicly funded MCV4 vaccine in Ontario. With respect to occupational groups, the responsibility rests with employers and, as with other travel vaccines, meningococcal vaccines are not publicly funded for travelers.

The joint statement notes that NACI was unable to provide a stronger recommendation than “should be considered” among individuals with high-risk medical conditions, due to limited evidence of the efficacy and safety of 4CMenB vaccine, as the vaccine has not yet been studied in these populations.

As noted above, there are no cost-effectiveness analyses within these populations and no Ontario data on rates of IMD within these groups. However, based on data obtained from the MOHLTC, the annual number of individuals who receive meningococcal vaccines on the basis of eligible high-risk medical conditions are relatively small. For example, over the course of the fiscal years of 2012–13 and 2013–14, a net number of approximately 600 doses of vaccines providing protection against serogroups A, C, Y, and W-135 were distributed for the immunization of high-risk clients in Ontario (Ontario Government Pharmacy and Medical Supply Service data, obtained via Dianne Alexander, personal communication, April 29, 2014).
4CMenB Vaccine for use in IMD contact management

Current Canadian guidance for the public health management of IMD includes immunoprophylaxis (immunization) and chemoprophylaxis for close contacts of cases. The purpose of chemoprophylaxis is to eradicate nasopharyngeal \textit{N. meningitidis} carriage, thus preventing subsequent disease in contacts and transmission to susceptible persons. Close contacts with ongoing exposure to a case should additionally receive immunization with serogroup-specific meningococcal vaccine if disease is caused by a vaccine-preventable serogroup. The rationale for immunoprophylaxis is that an increased risk of IMD persists for up to one year for household contacts, despite chemoprophylaxis.

There is some variability among international guidelines for IMD management regarding the role of immunoprophylaxis beyond chemoprophylaxis. The European Centre for Disease Prevention and Control also strongly recommends that household contacts receive immunoprophylaxis in addition to chemoprophylaxis, where disease is caused by a vaccine-preventable strain, unless the individual is considered to be protected by previous vaccination. Similarly, Australian guidelines recommend vaccination for unimmunized household and sexual contacts of cases of vaccine-preventable IMD, as soon as the serogroup is confirmed, and within four weeks of disease onset in the case, due to the prolonged risk of subsequent disease. The U.S. Advisory Committee on Immunization recommends only antibiotic chemoprophylaxis for close contacts of IMD cases.

Consistent with the other Canadian guidance documents on IMD management, including the Ontario Infectious Diseases Protocol, close contacts to be considered for immunoprophylaxis include:

- Household contacts
- Persons who have shared sleeping arrangements with a case
- Persons who have had direct nose or mouth contamination with oral or nasal secretions of a case (e.g., kissing, shared drinking bottles or cigarettes)
- Children and staff in child care or nursery schools where a case has been in attendance

The common guidance statement indicates that the advice for the use of 4CMenB vaccine in contact management is based on expert opinion and that it was unable to provide a stronger recommendation than “should be considered” for close contacts due to the limited evidence base regarding the use of the vaccine for this purpose. Currently, there is no direct evidence demonstrating use or effectiveness of 4CMenB vaccine in close contacts of serogroup B IMD cases who have also received chemoprophylaxis.

Despite the guidelines noted above, there is limited indirect evidence of the additional benefit of immunoprophylaxis, based on the risk of subsequent disease in close contacts after receiving antimicrobial chemoprophylaxis. Although chemoprophylaxis can reduce the risk of subsequent disease in household contacts within the first month by almost 90%, subsequent cases of serogroup B IMD among household contacts and in child care settings despite effective chemoprophylaxis have been documented. Subsequent cases may occur due to eradication failure or re-introduction of the infecting strain to susceptible contacts either by an unidentified contact or by the index case if not treated with an antibiotic that can eradicate nasal carriage. Symptom onset in these cases occurred as late as five months after the index case, illustrating prolonged risk of secondary disease.

In a systematic review and meta-analysis, Hoek et al. (2008) estimated the effectiveness of vaccination, in addition to chemoprophylaxis, in household contacts of IMD cases of all serogroups. In six large observational studies, 23 subsequent cases were reported among 19,529 household contacts given appropriate
chemoprophylaxis, of which more than 90% occurred 14 days or more after onset of disease in the index case. The weighted average attack rate among household contacts given correct chemoprophylaxis was 1.1 cases per 1,000 household contacts (95% confidence interval 0.7–1.7) in the 14 to 365 days after the index case. Assuming a vaccine efficacy of 85–95% during this time period, between 638 and 1,678 contacts would need to be vaccinated (in addition to chemoprophylaxis) to prevent one case of vaccine-preventable IMD. The number needed to vaccinate (NNV) to prevent one IMD death was estimated between 6,382 and 33,560 household contacts.

More recently, Ladhani et al. of Public Health England (PHE) (2014) estimated the NNV for household contacts receiving 4CMenB using data from Hoek et al. (2008) and assuming 73% vaccine coverage of all meningococcal strains (including non-B capsular groups) and 50% protective titres at 10 to 14 days after one dose of vaccine. If the vaccine is administered within four days of diagnosis of the index case, before receiving strain-typing results, the NNV would be 2,500; at 88% strain coverage, the NNV would be 2,104. PHE recommended that 4CMenB should not be routinely offered to household contacts or contacts in an educational setting, even if the strain is subsequently found to be vaccine-preventable. The rationale for this recommendation was as follows: PHE’s conclusion that the NNV is very high; the number of secondary cases, particularly late secondary cases, was judged to be very low; and 4CMenB may not provide adequate protection rapidly enough after a single dose, especially among young children. If a second case occurs in the same family, PHE states that 4CMenB should be offered in addition to chemoprophylaxis for all household contacts, even if more than 30 days have elapsed between cases and/or if the strains are found to be different. PHE advises both 4CMenB and MCV4 should be offered to high-risk household contacts (asplenia, splenic dysfunction or known complement deficiency) if not previously immunized or partially immunized after a single case occurs. The PHE document also outlines considerations around use of 4CMenB vaccine for confirmed clusters or community-based outbreaks.

Given how recently the common guidance statement was issued it was challenging to perform an environmental scan of P/T practices with respect to use of 4CMenB vaccine. The only P/T where information could be readily found online was Quebec, where the use of 4CMenB vaccine for contact management of cases of serogroup B IMD was described within the context of messaging to support an age-specific program in a region with particularly high incidence of disease (see “4CMenB Vaccine use in outbreak control” section below).

Should the MOHLTC decide to adopt the NACI/MBPPTG advice of implementing a 4CMenB vaccine program for contact management, an important programmatic perspective for the MOHLTC to consider, given the multiple dose schedule of the vaccine, is the number of doses that would be publicly funded for contact management. Given that the risk of IMD remains elevated among close contacts, particularly household contacts, for up to one year, it would be advisable to complete the full series for effective immunoprophylaxis. For the youngest of infants who are exposed as household contacts, this could theoretically provide a rationale for forgoing the public funding of the booster dose between 12 and 23 months of age if the vaccine series is initiated for IMD contact management. However, if this schedule is followed, it would be outside of the recommendations of the product monograph.

A related issue is that although the product monograph contains an age indication of 2 months to 17 years of age, the common guidance statement recommendations do not specify an upper age limit for use of 4CMenB vaccine for contact management. This is consistent with NACI advice for the use of other meningococcal vaccines for contact management despite the authorization of MCV4 products to a maximum age of 55 years of age and a minimum age of 9 months, 12 months, or 2 years, depending on the specific product. The 4CMenB vaccine has been evaluated in healthy adults aged 18 to 55 years and found to be safe and immunogenic using a schedule of two doses given at least one month apart, although the number of adults enrolled in these studies is small (fewer than 100 adult participants).
4CMenB Vaccine for use in outbreak control

Specific advice on the use of the vaccine for outbreak control and cluster management is outside the scope of this document. Decision-making regarding vaccine use for outbreak control will involve a number of considerations specific to the outbreak or cluster, such as age-specific attack rates, links between cases, dates of onset, defining the population at risk, and molecular information on the specific meningococcal strain.

Bexsero® has been used for outbreak control in two distinct university outbreaks in the United States, under special access to the vaccine, as the vaccine is not currently licensed in that country. Within the Canadian context, a 4CMenB vaccine campaign was introduced in late April 2014 targeting individuals aged 20 years and younger and those who attend an educational institution within the region of Saguenay-Lac-Saint-Jean. Since 2003, the serogroup B clone ST-269 has represented a high proportion of serogroup B disease in Eastern Quebec, in particular the regions of Saguenay-Lac-Saint-Jean, Capitale-Nationale, and Chaudière-Appalaches. The incidence of serogroup B disease in Saguenay-Lac-Saint-Jean is particularly high among those under 20 years of age (11.5 per 100,000 population), as compared to the provincial incidence in Quebec of 2.1 per 100,000 population over the same period of 2006 to 2013. Based on this epidemiology and other considerations, the immunization committee of Quebec unanimously recommended the introduction of a 4CMenB vaccine program within the Saguenay-Lac-Saint-Jean region and ongoing enhanced IMD surveillance within the rest of the province.
PIDAC-I options for consideration with respect to 4CMenB Vaccine immunization program decision-making

PIDAC-I supports the process used to develop the common guidance statement on 4CMenB vaccine and supports the recommendations for vaccine use contained within the document. In light of the NACI/MBPPTG recommendations, PIDAC-I is outlining the following options for consideration regarding 4CMenB immunization program decision-making.

1. Implementation of a publicly funded routine immunization program using 4CMenB vaccine

   - PIDAC-I supports the recommendation not to implement a publicly funded routine 4CMenB immunization program. No cost-effectiveness analysis has found the introduction of a routine, publicly funded 4CMenB vaccine program to be cost-effective using commonly used thresholds. In the Ontario analysis by Tu et al., even with a vaccine price of zero dollars, a program would still exceed such thresholds. Economic models are extremely sensitive to disease incidence and assumptions regarding herd immunity. If disease incidence within Ontario significantly rises in the future and/or if future evidence becomes apparent regarding herd effects from other jurisdictions, cost-effectiveness models may need to be revisited.

2. Routine prophylactic administration of acetaminophen at the time of 4CMenB vaccination

   - PIDAC-I supports the recommendation contained with the common guidance statement that prophylactic administration of acetaminophen at the time of vaccination with this vaccine may be considered to prevent fever in infants and children under the age of 3 years. PIDAC-I supports this recommendation regardless of vaccine indication (i.e., private purchase of vaccine for primary prevention, use of vaccine for IMD contact management, or use among those at higher risk of IMD).

3. Use of 4CMenB vaccine for individuals with medical conditions at higher risk of IMD

   - PIDAC-I supports the recommendation contained within the common guidance statement that the use of 4CMenB vaccine should be considered for individuals with high-risk medical conditions.
   - PIDAC-I supports adding the 4CMenB vaccine to existing Ontario recommendations to provide protection using MCV4 vaccine in these populations.
   - PIDAC-I supports including all groups identified by NACI to be at higher risk for meningococcal disease within future Ontario decision-making, including those with acquired complement deficiency and those with HIV infection.
4. Use of 4CMenB vaccine for close contacts of cases of serogroup B IMD

- PIDAC-I supports the recommendations contained within the common guidance statement that the use of 4CMenB vaccine should be considered, in addition to chemoprophylaxis for close contacts of cases of serogroup B IMD, as part of routine IMD case management. This would be consistent with existing Ontario guidelines to offer immunoprophylaxis in addition to chemoprophylaxis, to close contacts for vaccine-preventable serogroups of IMD.
- PIDAC-I supports that 4CMenB be publicly funded for this purpose
- PIDAC-I supports the language contained within the common guidance document which does not limit use of vaccine to IMD contacts within the age range specified in the product monograph. PIDAC-I supports the use of vaccine for management of close contacts two months of age and older, with no upper age limit specified for these contacts.
- In addition, PIDAC-I supports providing close contacts of serogroup B IMD with a full series of vaccine according to age, as opposed to one dose, in order to provide longer-term protection in keeping with the longer-term increased risk of IMD among household contacts.

5. Use of 4CMenB vaccine for outbreak management

- As noted above, advice for the use of 4CMenB vaccine in any future Ontario outbreaks will occur at a future date and would be based on outbreak-specific epidemiology and information on strain susceptibility based on the MATS assay.
- PIDAC-I encourages PHO to monitor the published and grey literature with respect to the use of the vaccine within outbreaks, in particular its use in young adult populations who are older than the current age indication of the vaccine product.

Other areas of consideration suggested by PIDAC-I as it relates to 4CMenB vaccine include:

6. IMD surveillance

- PIDAC-I encourages PHO to continue to conduct enhanced surveillance of serogroup B IMD through the use of integration of PHOL isolates and reportable disease information. Ongoing monitoring of serogroup B IMD incidence is important to ensure Ontario’s programs are informed by the most up-to-date evidence of disease burden.
- PIDAC-I encourages PHOL and the National Microbiology Laboratory, in collaboration with other partners as required, to further characterize the strain coverage provided by the 4CMenB vaccine, ideally using a non-proprietary assay.

7. 4CMenB AEFI surveillance

- In the absence of a publicly funded routine immunization program, many clinicians will recommend the 4CMenB vaccine and many parents will elect to privately purchase the vaccine. As with any new vaccine program, PIDAC-I encourages such clinicians to report AEFIs, and PHO to
carefully monitor AEFIs associated with the 4CMenB vaccine in Ontario and to contribute to the future body of literature on post-marketing safety surveillance of the vaccine.

- PIDAC-I also encourages PHO to monitor 4CMenB AEFI reports reported in the peer-reviewed and grey literature and through PHO’s participation in Canada’s Vaccine Vigilance Working Group.

8. Research

- PHO is encouraged to continue to monitor the evolving research on the effectiveness, immunogenicity, strain coverage, impact on carriage, and duration of protection provided by the vaccine.
References


