Immunization for meningococcal serogroup B: What does the practitioner need to know?

Joan L Robinson; Canadian Paediatric Society, Infectious Diseases and Immunization Committee

Français en page 95

Most invasive meningococcal disease in Canada is now caused by serogroup B organisms. A vaccine directed against this serogroup (4CMenB) is newly licensed in Canada. A decision will need to be made by all provinces and territories regarding whether a routine infant immunization program is warranted. This decision will need to take into account factors such as uncertain estimates for the effectiveness of the vaccine, the high incidence of fever from the vaccine and the burden of introducing more injections into the current immunization schedule, and consider them against the potentially preventable mortality and morbidity that result from a rare but very serious disease.

Key Words: Meningococcal; Serogroup B; Vaccine

There are 12 serogroups of *Neisseria meningitidis*, as determined by the polysaccharide capsule of the bacterium, with most invasive meningococcal disease (IMD) caused by serogroups A, B, C, Y and W. Since the 1940s, IMD in Canada and the United States has been predominantly caused by serogroups B, C and Y. All provinces and territories have implemented routine infant immunization against serogroup C. Alberta, Saskatchewan, Ontario, New Brunswick, Prince Edward Island, and Newfoundland and Labrador have recently introduced routine immunization programs for adolescents using the quadrivalent (A, C, Y and W) conjugate vaccine. Case data analyzed by the Public Health Agency of Canada show that serogroup B (MenB) is now the most prevalent serogroup in Canada, accounting for >50% of cases between 2002 and 2011 (see Figure 2 at www.phac-aspc.gc.ca/im/vpd-mev/meningococcal-eng.php). (1) The majority of cases occur in preschool-age children (Table 1). (2) A four-component vaccine for MenB (4CMenB or Bexsero, Novartis, Canada) was licensed in Canada in December 2013. Provinces and territories, clinicians and parents will need to determine when immunization is warranted.

The following evidence should be considered to determine if and when immunization is warranted.

WHAT IS THE PREDICTED EFFECTIVENESS OF 4CMenB?

There have been clinical studies conducted with 4CMenB administered at: two, four and six months of age (3,4); two, three and four months of age (3); 12 to 15 months of age (two doses two months apart) (5); and 11 to 17 years of age (one to three doses). (6) Because MenB infection is rare, studies cannot provide efficacy data. It would require years of surveillance in a large population with routine immunization to establish vaccine effectiveness. Therefore, decisions to vaccinate must depend on evidence from correlates of protection (ie, immune markers that correlate with protection).

La vaccination contre le méningocoque du sérotype B : ce que le praticien doit savoir

Au Canada, la plupart des méningocoques invasives sont désormais causées par des organismes du sérotype B. Un vaccin conçu contre ce sérotype (4CMenB) vient d'être homologué au Canada. Toutes les provinces et tous les territoires devront décider si un programme de vaccination systématique des nourrissons est justifié. Cette décision devra tenir compte de certains facteurs, tels que les évaluations incertaines de l'efficacité du vaccin, l'incidence élevée de fièvre causée par le vaccin et le fardeau lié à l'introduction d'injections supplémentaires dans le calendrier de vaccination actuel, puis les comparer à la mortalité et à la morbidité potentiellement évitables découlant d'une maladie rare, mais très grave.

Unfortunately, correlates of protection are yet to be established for MenB. Unlike other meningococcal serogroups, group B does not elicit a response to the polysaccharide capsule. The capsule of MenB strains cross-reacts with human fetal neural tissue. This cross-reaction is not known to be harmful, but it renders the capsule nonimmunogenic. The MenB vaccine was developed by identifying subcapsular proteins expressed on the surface of many strains of meningococcus that could elicit an immune response. The four components thus identified and combined with alum as an adjuvant in 4CMenB include: neisserial heparin-binding antigen (NHBA), factor H-binding protein (fHbp), neisserial adhesion A (NadA) and PorA (the most immunogenic protein from the outer membrane vesicles). A vaccine containing only PorA successfully controlled an outbreak of IMD in New Zealand; however, there are too many antigenic variants of PorA to allow for a universal vaccine based on this protein alone. (7)

Using test strains that contained only one of the four vaccine components, the studies previously mentioned assessed the immunological response postimmunization to fHbp, NadA and PorA by determining the serum bactericidal titre using human complement (hSBA) to that component. (3,6) An hSBA titre of at least 1:4 to the polysaccharide capsule is an established correlate of protection for other meningococcal vaccines; therefore, this titre was applied. Following the 4CMenB series, almost all patients in all studies had protective hSBA titres to fHbp and NadA. Almost all adolescents (6) and approximately 85% of infants (3,4) had protective titres to PorA. Only 100 infants had hSBA titres measured for NHBA because it has been more difficult to develop this assay, but 84% developed protective titres. (4) With doses at two, four and six months of age, protective titres were maintained to fHbp in 81% of children, NadA in 99%, PorA in 22% and NHBA in 61% at 12 months of age; a booster then yielded titres similar to those following the

Correspondence: Canadian Paediatric Society, 2305 St Laurent Boulevard, Ottawa, Ontario K1G 4J8. E-mail info@cps.ca, website www.cps.ca

TABLE 1
Outcome of Canadian children with meningococcal serogroup B infection in 12 Canadian tertiary care paediatric hospitals, 2002 through 2011

Age group	Death, n (%)	Any sequelae, n (%)	Amputation	Skin scarring	Renal dysfunction	Deafness	Seizures requiring anticonvulsants at discharge	Other neurological sequelae
<1 year (n=80)*	3 (4)	20 (26)	3	3	1	9	8	4 [†]
1 to 4 years (n=99)	4 (4)	26 (27) [‡]	7	13	1	9	2	3 [§]
5 to 19 years (n=99)	5 (5)	10 (11)	0	4	0	3	0	2 [¶]

Data presented as n unless otherwise indicated. Some children experienced more than one type of sequelae. Percentages for sequelae are calculated for survivors only. *57 were <6 months of age and 23 were six to 11 months of age (personal communication, J Bettinger); [†]Visual loss from endophthalmitis; hypotonia; shunts for subdural effusions; subdural empyema; [‡]One child had avascular necrosis of the femoral head which is not listed elsewhere; [§]Swallowing difficulties requiring gavage feeding; paralysis; not specified for the third case; [¶]Quadriplegia with brain stem and cerebellar infarcts; decreased mobility affecting daily living. Data adapted from reference 1

six-month dose for all four components.(4) When measured approximately two years after this fourth dose, protective titres were maintained to fHbp in 65% of children, NadA in 76%, PorA in 41% and NHBA in 67%.(8) Decreases in antibody titres for vaccines given concomitantly were shown for pertactin (contained in some pertussis vaccines),(3) pneumococcus serotype 6B(3) and type 2 polio,(4) but these decreases were not believed to be clinically significant.

Strains of MenB do not all express components of 4CMenB. To predict whether 4CMenB will protect against a given strain, a Meningococcal Antigen Typing System (MATS) has been developed. MATS attempts to determine, using enzyme-linked immunoabsorbent assay (ELISA), whether the concentration of fHbp, NadA and NHBA in strains of MenB are sufficient that the immune response following 4CMenB would be predicted to protect against that strain. For PorA, MATS simply measures the presence or absence of the matching variant of PorA because this protein is highly immunogenic.(7) MATS testing of 157 Canadian IMD strains in 2006 through 2009 predicted that 66% of strains (95% CI 46 to 78) would be covered by 4CMenB (26% matched one, 29% matched two and 11% matched three antigens).(9) It will only be possible to prove the predictive value of MATS testing when it becomes evident which strains of MenB cause IMD in vaccinated children.

All four components of 4CMenB vaccine may be present in non-B serogroups; it is, therefore, possible that effectiveness could extend beyond MenB.(4) 4CMenB could also be more effective than predicted if there is a significant herd effect, as appears to be likely for conjugate meningococcal A and C vaccines.(10,11) A decrease in carriage rates would predict a herd effect, but there was only a 16.5% (95% CI 1.5 to 29.2) decline in carriage rates when university students were immunized in England.(12)

In summary, estimates of effectiveness are still very tentative.

WHAT ARE POTENTIAL BARRIERS TO USING 4CMenB?

Number of required doses

The bulk of MenB disease occurs in young children, with approximately 70% of cases in the first year of life occurring in infants younger than six months of age.(2,13) Vaccine administration at two, four and six months of age may not confer significant protection until six months of age, although again, herd effect may protect younger infants.

There are no data regarding the persistence of vaccine-induced immunity. For most infections, a brisk anamnestic response following exposure often confers protection in individuals with waning antibody titres. However, IMD progresses so rapidly that there may not be time for an anamnestic response to occur. Thus, for

protection, individuals may need a constant high level of circulating antibody. It is, therefore, likely that boosters would be required to protect throughout childhood.

Adverse events

Fever is the only clinically significant adverse event recognized to date with 4CMenB. When combined with routine vaccines, a rectal temperature >38.5°C occurred within 6 h postimmunization in 65% of infants at two, four or six months of age, compared with 32% receiving routine vaccines alone.(4) This fever persisted for >24 h in approximately two-thirds of cases. Fever is of particular concern at two months of age because a septic work-up and admission for empirical intravenous antibiotics are commonly advised in this age group for fever with no definite source. Another study involving infants reported outcomes according to age group: 563 of 941 infants (59%) who received 4CMenB and routine vaccines at two months of age had an axillary temperature of 38.0°C, versus 96 of 311 (31%) who received routine vaccines alone and 238 of 627 (38%) who received 4CMenB alone.(3) In an open-label study in which parents were presumably advised to expect fever, only 28 of 1966 infants (1.4%) who received 4CMenB plus routine vaccines were brought to medical attention because of fever, compared with 12 of 659 (1.8%) in the routine vaccine group.(4) It is unclear whether assuming that a fever that persists beyond 24 h is vaccine related and benign at two months of age is a safe policy. Antipyretics have been shown to blunt the height of the fever without dampening the immune response to 4CMenB,(14) but the concern remains that medication could mask fever from a coincidental invasive bacterial infection.

IS THE BURDEN OF DISEASE FROM MenB SUFFICIENTLY HIGH TO JUSTIFY A VACCINE?

Data were collected for 2002 through 2011 from 12 paediatric tertiary care centres by the Canadian Immunization Monitoring Program, Active (IMPACT), yielding a mortality rate of three of 80 cases (3.8%) in infants younger than one year of age, and nine of 198 cases (4.5%) in children and adolescents one through 19 years of age. Intensive care admission occurred for 169 of 278 cases (61.0%).(2) Sequelae at discharge are presented in Table 1. In 2000 through 2010, the mortality rate for MenB in Ontario was seven of 52 cases (13.5%) in infants younger than one year of age and four of 85 cases (4.7%) in children and adolescents one through 19 years of age.(13) A case-control study investigating 245 of 618 paediatric survivors of Men B in England a median 3.75 years following IMD showed that 21 of 244 cases (9%) and six of 328 controls (2%) had major deficits: full-scale IQ <70, seizures, bilateral sensorineural hearing loss of 40 dB or more, disabling

motor impairment, significant visual loss or major communication disability ($P < 0.05$). Any deficit (the major deficits listed above plus full-scale IQ 70 to 85, minor or unilateral sensorineural hearing loss, single-digit amputation, minor communication deficit or psychological disorders) occurred in 87 of 244 cases (36%) and 49 of 328 controls (15%) ($P < 0.05$).⁽¹⁵⁾

Extrapolating from data in the Ontario study cited above, if 4CMenB prevents 70% of IMD in children younger than 12 months of age, practitioners would have to vaccinate more than 38,000 children to prevent one case. However, if three doses administered at two, four and six months of age are required for protection, infants younger than six months of age will remain unprotected; therefore, this number increases to more than 141,000⁽¹³⁾ (and approximately 10 to 20 times that number to prevent one death). The number needed to vaccinate will be lower than these estimates if the vaccine yields a herd effect or covers some non-B strains, or if there are a significant number of culture-negative cases not detected by surveillance.⁽⁷⁾ The number will be higher if there is emergence of clones that are not well matched with vaccine strains.⁽¹⁶⁾

WHO SHOULD RECEIVE THE VACCINE?

The highest risk for IMD occurs in patients with asplenia or hyposplenism, congenital complement, properdin, factor D or primary antibody deficiencies, in individuals prescribed the terminal complement inhibitor eculizumab (Soliris, Alexion Pharma Canada, Canada) or who have had more than one

episode of IMD, and in laboratory personnel who work with the organism. All high-risk individuals should be offered 4CMenB when it is available. It is less clear whether military personnel and individuals with HIV should be routinely offered the vaccine.

A recommendation from the National Advisory Committee on Immunization (NACI) regarding optimal use is pending. If routine use is recommended, physicians should mention the new vaccine to parents of children in the most vulnerable age group at well-child visits, even if it is not publicly funded.⁽¹⁷⁾

CONCLUSION

An effective vaccine for serogroup B could prevent the majority of IMD in Canada, but it will take years to determine the efficacy of 4CMenB. Now that 4CMenB is licensed in Canada, it should be offered to individuals at highest risk of IMD. Pending the NACI decision on routine use of 4CMenB, it is hoped that this document will be useful to clinicians when faced with questions from parents. If routine use is recommended by NACI, clinicians are obligated to discuss the vaccine with the parents of children in the age group targeted for routine use at each well child visit.

Note: Information for parents, 'Meningococcal vaccine', can be accessed at www.caringforkids.cps.ca.

ACKNOWLEDGEMENTS: This practice point was reviewed by the Community Paediatrics Committee of the Canadian Paediatric Society.

REFERENCES

- Public Health Agency of Canada, 2012. Invasive meningococcal disease (IMD), Figure 2: www.phac-aspc.gc.ca/im/vpd-mev/meningococcal-eng.php (Accessed December 16, 2013).
- Bettinger JA, Scheifele DW, Le Saux N, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J* 2013;32(1):e20-5.
- Gossger N, Snape MD, Yu LM, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: A randomized controlled trial. *JAMA* 2012;307(6):573-82.
- Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: Results of two randomised trials. *Lancet* 2013;381(9869):825-35.
- Prymula R, Vesikari T, Esposito S, et al; Meningococcal B Infant Vaccine Study Group. Catch-up vaccination of healthy toddlers with an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) – Exploration of a two-dose schedule. European Society for Paediatric Infectious Diseases Conference, June 7 to 11, 2011, The Hague, The Netherlands.
- Santolaya ME, O'Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: A phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet* 2012;379(9816):617-24.
- Major M, Moss S, Gold R. From genes to vaccine: A breakthrough in the prevention of meningococcal group B disease. *Paediatr Child Health* 2011;16(8):e61-4.
- Snape MD, Saroey P, John TM, et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. *CMAJ* 2013;185(15):E715-24.
- Bettinger JA, Scheifele DW, Halperin SA, et al; For the members of the Canadian Immunization Monitoring Program, Active (IMPACT). Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4CMenB). *Vaccine* 2013;32:124-30.
- Kristiansen PA, Diomandé F, Ba AK, et al. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. *Clin Infect Dis* 2013;56(3):354-63.
- Campbell H, Andrews N, Borrow R, Trotter C, Miller E. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: Effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clin Vaccine Immunol* 2010;17(5):840-7.
- Read RC, Baxter D, Chadwick DR, et al. Impact of a quadrivalent conjugate (MENACWY-CRM) or a serogroup B (4CMENB) meningococcal vaccine on meningococcal carriage in English university students. Abstract 1472. European Society for Paediatric Infectious Disease Annual Conference. Milan, May 28 to June 1, 2013.
- Dang V, Jamieson FB, Wilson S, et al. Epidemiology of serogroup B invasive meningococcal disease in Ontario, Canada, 2000 to 2010. *BMC Infect Dis* 2012;12:202.
- Prymula R, Esposito S, Kittel C, Kohl I, Toneatto D, Dull P. Prophylactic paracetamol in infants decreases fever following concomitant administration of an investigational meningococcal serogroup B vaccine with routine immunisations. Poster 631. European Society for Paediatric Infectious Disease Annual Meeting. The Hague, June 7 to 10, 2011.
- Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): A case-control study. *Lancet Neurol* 2012;11(9):774-83.
- Zhou J, Lefebvre V, Deng S, et al. Invasive serogroup B *Neisseria meningitidis* in Quebec, Canada, 2003 to 2010: Persistence of the ST-269 clone since it first emerged in 2003. *J Clin Microbiol* 2012;50(5):1545-51.
- Canadian Medical Protective Association, 2009 (IS0887-E). New vaccines – What are your obligations?: An article for physicians by physicians: www.cmpa-acpm.ca/cmpapd04/docs/resource_files/infosheets/2008/com_is0887-e.cfm (Accessed November 12, 2013).

CPS INFECTIOUS DISEASES AND IMMUNIZATION COMMITTEE

Members: Robert Bortolussi (past Chair); Natalie A Bridger MD; Jane C Finlay MD (past member); Susanna Martin MD (Board Representative); Jane C McDonald MD; Heather Onyett MD; Joan L Robinson MD (Chair); Marina I Salvadori MD (past member); Otto G Vanderkooi MD

Consultant: Noni E MacDonald MD

Liaisons: Upton D Allen MD, Canadian Pediatric AIDS Research Group; Michael Brady MD, Committee on Infectious Diseases, American Academy of Pediatrics; Janet Dollin MD, College of Family Physicians of Canada; Charles PS Hui MD, Committee to Advise on Tropical Medicine and Travel (CATMAT), Public Health Agency of Canada; Nicole Le Saux MD, Immunization Monitoring Program, ACTive (IMPACT); Dorothy L Moore MD, National Advisory Committee on Immunization (NACI); John S Spika MD, Public Health Agency of Canada

Principal author: Joan L Robinson MD

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. All Canadian Paediatric Society position statements and practice points are reviewed on a regular basis. Retired statements are removed from the website. Please consult the Position Statements section of the CPS website (www.cps.ca) for the full-text, current version.