



Investigational Use of Meningococcal Serogroup B Vaccine

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N *isseria meningitidis* is a significant cause of sepsis and meningitis throughout the world. In sub-Saharan Africa, periodic epidemics result in a rate of invasive meningococcal disease ranging from 10 to 1,000 cases per 100,000 patients and in New Zealand an ongoing epidemic has produced annual infection rates as high as 17 cases per 100,000 patients.¹ While the incidence of invasive meningococcal disease is much lower in North America and Europe (0.5-3 cases per 100,000), the fatality rate remains at 5-15% even with early initiation of antibiotics. In addition, 10-20% of survivors experience permanent sequelae as a result of their infection. In the United States, infants and children less than 5 years of age are the most likely to be affected, but adolescents are often at risk during outbreaks.^{1,2}

Of the thirteen *N. meningitidis* serogroups identified, six are responsible for the majority of invasive cases: A, B, C, W, X, and Y. The currently available quadrivalent meningococcal capsular polysaccharide conjugate vaccines, Menveo[®] and Menactra[®], provide coverage for serogroups A, C, W, and Y. They do not include coverage for B because of the poor immunogenicity of the serogroup B polysaccharide capsule. In 2012, 20% of invasive meningococcal cases reported to the Centers for Disease Control and Prevention (CDC) were caused by serogroup B. In Canada, serogroup B accounted for 62% of reported invasive meningococcal disease in 2011, with an average of 111 cases reported annually between 2007 and 2011, while in England and Wales, serogroup B accounts for approximately 60% of meningococcal disease in children less than 5 years of age.¹⁻⁴

In January 2013, the first four-component meningococcal serogroup B (4CMenB) vaccine, Bexsero[®] (Novartis Vaccines), was approved by

the European Medicines Agency.⁵ It has also been approved in Canada and Australia. While not yet approved in the United States, the Food and Drug Administration (FDA) allowed the use of Bexsero[®] during meningococcal serogroup B outbreaks at Princeton and the University of California, Santa Barbara (UCSB) under an Investigational New Drug application. In February and March 2014, more than 5,000 Princeton students and over 9,000 UCSB students received the vaccine.

A second meningococcal serogroup B vaccine is being developed by Pfizer. In the first quarter of 2014, both vaccines were given a Breakthrough Therapy designation by the FDA.⁶ This classification provides a mechanism for expedited review of products for serious or life-threatening diseases in the United States. Both companies submitted their Biologics License Applications to the FDA in June.

Vaccine Development

N. meningitidis serogroup B has distinct differences from the other common serogroups. Unlike the other serogroups of the quadrivalent conjugate vaccine, its polysaccharide capsule is not highly immunogenic. The capsule is a homoliner polymer of $\alpha(2\rightarrow8)$ N-acetylneuraminic acid which is also expressed on human fetal neural cells. Inducing an immune response to this substance during infancy could potentially alter axon guidance, synaptic plasticity, and cell migration in the developing brain. Previous attempts at creating a serogroup B vaccine from extracted subcapsular proteins or outer membrane vesicles (OMV) have been successful in providing coverage for only a single strain, limiting their utility to only those outbreaks caused by the susceptible strain.¹⁻⁸

The vaccine being developed by Pfizer, Bivalent rLP2086, targets factor H binding protein

(fHbp), a surface-exposed lipoprotein found in pathogenic *N. meningitidis* isolates. It includes two fHbp variants, each containing one of the two most common amino acid sequences for this protein. This vaccine is currently in phase 2 studies, and as a result, there is limited data available on its safety and efficacy in the literature.

The Bexsero® 4CMenB vaccine was developed with an innovative approach termed reverse vaccinology.⁷⁻⁹ This technique was made possible as a result of whole genome sequencing of meningococcal serogroup B strain MC58. Screening revealed 570 potential surface expressed antigens; three identified as playing a significant role as virulence factors in meningococcal disease were incorporated into the vaccine: fHbp, *Neisseria* heparin binding antigen (NHBA), and *Neisseria* adhesion A (NadA). The fourth component of the vaccine, OMV PorA serosubtype P1.4 from the NZ98/254 strain responsible for the current New Zealand outbreak, was added to further broaden its coverage.

Preclinical testing suggests this combination will induce antibody production to 78% of serogroup B strains.¹⁰ The extent of coverage has also been assessed with the Meningococcal Antigen Typing System (MATS).^{11,12} In 2013, investigators from the Vaccine Evaluation Unit of Public Health England using this simulation technique predicted coverage of 70% of expected meningococcal serogroup B strains (95% CI 55-85%), based on those reported in England and Wales during 2007 and 2008.¹¹ Earlier this year, a collaborative group from Canada predicted overall coverage of 66% (95% CI 46-78%) based on serogroup B strains reported through the Canadian Immunization Monitoring Program Active (IMPACT) from 2006 to 2009.¹²

Seroresponse

With the low incidence of meningococcal-related illness in most countries, the effectiveness of a vaccine in preventing invasive disease is difficult to establish. As with the quadrivalent meningococcal vaccines already on the market, the efficacy of the 4CMenB vaccine has been established using antibody titers as a surrogate marker. Data on the immunologic response to 4CMenB was gathered from samples obtained in multicenter randomized, controlled clinical trials of patients from 2 months to 50 years of age.⁵ Seroresponse was defined as the percentage of patients who achieved a serum bactericidal assay (hSBA) titer ≥ 5 .

In composite data for infants, children, and adults, seroresponse one month after completion of the immunization series was 95-100% for the fHbp, NadA, and PorA P1.4 antigens. Seroresponse to the heparin binding antigen (NHBA) was above 95% in all groups except children 12-23 months of age, who had a rate of only 63% after a 2-dose primary series. Antibody titers declined significantly by 1 year following immunization, but increased to target levels after administration of a booster dose.

Three of the premarketing 4CMenB clinical trials used to provide the composite data have been published. In 2012, Gossger and colleagues described the results of a phase 2b multicenter, open-label, parallel-group randomized controlled study of 1,885 infants.¹³ Patients were enrolled at 2 months of age and were randomized to one of four groups: 1) 4CMenB immunization at 2, 4, and 6 months with their routine immunizations, 2) immunization with 4CMenB at 2, 4, and 6 months with their other immunizations given at 3, 5, and 7 months, 3) 4CMenB immunization at 2, 3, and 4 months with routine immunizations (an accelerated schedule), or 4) routine immunizations alone. The primary outcome was the percentage of patients with serum bactericidal activity titers ≥ 5 against three meningococcal serogroup B strains. After the three-dose 4CMenB series, 99-100% of patients achieved target titers for two of the strains and 79-86% achieved target titers for the third strain. There were no significant differences in response between the groups who received 4CMenB with other immunizations or alone and no differences between the traditional and accelerated immunization schedules.

The most commonly reported adverse effect after vaccination was fever. The incidence of fever $\geq 38.0^\circ\text{C}$ was higher in the infants given 4CMenB with other vaccines (51-61%) than when given alone (26-41%), or when routine vaccines were given without 4CMenB (23-36%). Seizures were reported in four patients (three in the 4CMenB groups). There were two patients who experienced hypotonic hyporesponsive episodes (one following 4CMenB) and two cases of Kawasaki disease (one possibly related to 4CMenB).

Vesikari and colleagues, writing as the EU Meningococcal B Infant Vaccine Study group, published results from two of the randomized studies conducted with 4CMenB vaccine.¹⁴ Primary immunization was studied in 2,627 infants enrolled in an open-label study and 1,003 in a blinded study. A total of 1,555 infants were enrolled in a study of response to a booster dose.

Patients were randomized to 4CMenB plus routine immunizations, meningococcal C vaccine plus routine immunizations, or routine immunizations alone. One month after the primary series, 100% of patients had hSBA titers ≥ 5 for strains selective for fHbp and NadA, and 84% had titers ≥ 5 for PorA P1.4. Immune response had waned by 12 months, but the booster dose brought titers back to 5 or greater in 95-100% of patients for all antigens. Fever was more common in the patients given 4CMenB, occurring in 77% of patients compared to 45% of those given routine immunizations alone and 47% of those given meningococcal C vaccine.

Contraindications and Precautions

Use is contraindicated in patients with known hypersensitivity to any component of the vaccine. It is recommended that 4CMenB vaccine not be given to patients with thrombocytopenia or other coagulation disorders who may experience complications from an intramuscular injection.⁵ Immunization should be postponed in patients who are experiencing an infection with fever. The 4CMenB vaccine has not been reported to produce toxicity in women who are pregnant or breastfeeding or their offspring, but use in this population should be carefully evaluated based on the benefit-risk ratio.

Adverse Effects

The 4CMenB vaccine has been administered to more than 8,000 infants, children, and adults during premarketing clinical trials.⁵ The most frequently reported adverse effects after administration in adolescents and adults are pain, swelling, or tenderness at the site of injection, myalgia and arthralgia, headache, fatigue, and nausea (occurring in $\geq 10\%$ of patients). In infants and children less than 10 years of age, the most common adverse effects associated with immunization were loss of appetite, drowsiness, irritability, unusual crying, diarrhea, vomiting, rash, fever (38.0-40° C), and swelling, tenderness, or redness at the site of injection (all reported in $> 10\%$ of patients). Higher fevers ($\geq 40^\circ$ C) and febrile seizures have been reported in 0.1-1% of patients. Prophylactic administration of antipyretics has been shown to reduce the incidence of post-vaccination febrile reactions.

As noted earlier, Kawasaki syndrome has been reported in pediatric patients after 4CMenB immunization, but the relationship to the vaccine has not been clearly established. Apnea has been reported in premature infants given 4CMenB; it is recommended by the manufacturer that all premature infants be monitored for apnea for 48-72 hours after vaccine administration.

Administration

The 4CMen B vaccine is indicated for use in infants 2 months of age and older, children, adolescents, and adults up to 50 years of age.⁵ Infants and children up to 2 years of age should receive a booster dose following their two or three dose primary series, according to the chart below. The need for a booster dose in older children or adults has not been established.

Infants 2-5 months

3 doses ≥ 1 month apart, with a booster dose at 12-23 months

Infants 6-11 months

2 doses ≥ 2 months apart, with a booster dose during the second year of life

Children 12-23 months

2 doses ≥ 2 months apart, with a booster dose 12-23 months after the primary series

Children 2-10 years

2 doses ≥ 2 months apart, no booster

Adolescents and adults

2 doses ≥ 1 month apart, no booster

The 4CMenB vaccine is available in Europe, Canada, and Australia in 0.5 mL pre-filled syringes with a 2-year shelf-life.⁵ The vaccine must be refrigerated until use and should be shaken prior to administration to form a homogenous suspension. It should be given as a deep intramuscular injection into the anterolateral aspect of the thigh in infants or the deltoid in older patients. It may be administered at the same time as other vaccines, including the quadrivalent meningococcal conjugate vaccine, but the injections should be given at separate sites. The tip cap of the syringe contains latex and the risk for allergic reactions should be considered in patients with a latex allergy.

Scope of Immunization

At this time, use of the still-investigational 4CMenB vaccine in the United States is limited to prophylaxis during outbreaks. Once approved by the FDA, it is expected that the Advisory Committee on Immunization Practices (ACIP) will meet to determine whether the vaccine should continue to be used only during outbreaks, as in Canada, or be adopted into the routine childhood immunization schedule.⁴ With the low incidence of invasive meningococcal disease and the cost involved, it may be difficult to justify routine immunization beginning in infancy.¹⁵ Research currently being conducted in England, however, may change perceptions of the vaccine's utility. The ability of a meningococcal serogroup B vaccine to produce herd immunity by preventing asymptomatic colonization of the oropharynx is being analyzed in 2,968 university students.¹⁶ While this may

show promise in eliminating meningococcal serogroup B disease caused by the strains used in making the vaccine, it could also result in a shift to other strains or *Neisseria* species.

Summary

The availability of a vaccine for *N. meningitidis* serogroup B is a significant advance in reducing the impact of sepsis and meningitis worldwide. While not yet approved by the FDA, the availability of this vaccine as an investigational product during outbreaks at two U.S. universities has demonstrated its benefit in controlling the spread of disease.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their June meeting:

1. Vedolizumab (Entyvio™) was added with restriction to Gastroenterology for outpatients with moderate to severe Crohn's disease and ulcerative colitis.
2. Ramucirumab (Cyramza™) was added with restriction to FDA-approved indications.
3. Chewable multivitamin (Centrum® Silver® Chewables) was added with restriction to patients with short gut, GI dysfunction that impairs micronutrient absorption and/or the inability to tolerate other oral formulations.
4. The restriction on prohibiting sodium bicarbonate-buffered lidocaine was removed. Sodium bicarbonate vials will not be used for compounding buffered lidocaine but will be acquired as pre-filled syringes.
5. Trastuzumab (Herceptin®) was restricted to outpatient use only.
6. The restriction on rituximab (Rituxan®) was amended to use per institutional guidelines.

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