Considerations for Use of Serogroup B Meningococcal (MenB) Vaccines in Persons at Increased Risk

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Outline

- Meningococcal vaccination recommendations for persons at increased risk
- Review of groups at increased risk for serogroup B meningococcal disease
- Summary of vaccine immunogenicity and safety
- GRADE outcomes
- Proposed policy option language

Current MenACWY Conjugate Vaccine Recommendations for Persons at Increased Risk

- **Routine vaccination of persons aged ≥2 months at increased risk for meningococcal disease, including:**
  - Persons with persistent complement component deficiencies[1]
  - Persons with anatomic or functional asplenia[2]
  - Microbiologists who are exposed routinely to isolates of *Neisseria meningitidis*
  - Persons at risk during a community outbreak attributable to a vaccine serogroup
  - Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
  - Unvaccinated or incompletely vaccinated first-year college students living in residence halls
  - Military recruits

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H,

[2]Including sickle cell disease

Two MenB Vaccines For Persons Aged 10–25 Years in the United States

- **Trumenba ® (Pfizer), 3-dose series (0, 2, 6 months)**
  - Components: fHbp subfamily A/v2,3; subfamily B/v1
  - Licensed in the U.S. on October 29, 2014
- **Bexsero® (Novartis), 2-dose series (0, 1–6 months)**
  - Components: fHbp subfamily B/v1, NhbA, NadA, Por A1.4
  - Licensed in the U.S. on January 23, 2015
  - Licensed in >30 countries for persons ≥2 months of age

Policy Options for Use of MenB Vaccines

- **Persons at increased risk, including:**
  - Persons with persistent complement component deficiencies
  - Persons with anatomic or functional asplenia
  - Microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak
- **Broader use of MenB vaccines in adolescents and college students**

Policy Options: Age-Groups to be Included for Persons at Increased Risk

- **Persons aged 10–25 years only**
  - Licensed age indication
- **Persons aged ≥2 months**
  - Bexsero® licensed for persons aged ≥2 months in other countries
  - Data not currently available for Trumenba® for children <10 years
  - Potential for expanded age indication in US in the future
    - Work Group will review data for persons aged 2 months–10 years and may propose expanded policy options for persons at increased risk in the future
- **Persons aged ≥10 years**
  - Goes beyond licensed indication but no theoretical differences in safety for those >25 years as compared to those 10–25 years

GROUPS AT INCREASED RISK FOR MENINGOCOCCAL DISEASE

Persons with Persistent Deficiencies in the Complement Pathway

- **Persistent (i.e., genetic) deficiencies in the complement pathway (e.g., C3, properdin, Factor D, Factor H, or C5-C9)**
  - Prevalence of ~0.03%[1] in general population
  - Up to 10,000-fold increased risk and can experience recurrent disease[2]

[1]P Densen. Complement deficiencies and meningococcal disease. Clin Exp Immunol. Oct 1991; 86(Suppl 1): 57-62.
[2]Cohn et al. Prevention and Control of Meningococcal Disease. MMWR. March 22, 2013; 62 (RR-2)

Eculizumab (Soliris®)

- Monoclonal antibody approved for treatment of atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH)
- Binds to C5 and inhibits the terminal portion of the complement cascade
- 5/326 subjects in a clinical trial developed meningococcal disease despite prior vaccination

> Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated [*see Adverse Reactions (6.1)*]. In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with Soliris [*see Adverse Reactions (6.1)*].

- Not explicitly included in MenACWY conjugate vaccine recommendations

http://soliris.net/sites/default/files/assets/soliris_pi.pdf

Persons With Functional or Anatomic Asplenia

- Appear to be at increased risk for meningococcal disease, however data are less compelling than for pneumococcal disease risk[1]
- Includes sickle cell disease which affects ~90,000-100,000 persons of all ages[2]
- Higher mortality rate (40%–70%)[3]
- Demonstrate significantly lower response to 1 dose of MenC vaccine[4]

[1]Cohn et al. Prevention and Control of Meningococcal Disease. MMWR. March 22, 2013; 62 (RR-2)
[2]http://www.cdc.gov/ncbddd/sicklecell/data.html
[3]Updated recommendations for the use of meningococcal conjugate vaccines . MMWR. January 28,2011; 60(3): 72-76.
[4]Balmer, P et al. Infection and Immunity, Jan 2004, 332-337

Case Reports of Laboratory Acquired Meningococcal Disease

- **Review by Sejvar et al. (2005)**
  - 16 cases worldwide 1985–2001
  - All occurred among clinical microbiologists in medical microbiology labs
    - 7 serogroup C, 9 serogroup B
    - None from hematology, chemistry, or research labs
  - 8 fatal (50%)
  - 15 cases strain manipulation performed on open lab bench
- **6 additional cases since this review**
  - 2 in US, 1 each New Zealand, France, Sweden, Argentina
  - Includes cases in industry and research microbiologists

Sejvar et al. Assessing the risk of laboratory acquired meningococcal disease. J Clin Microbiol 2005; 43:4811-4.
CDC. Laboratory-acquired meningococcal disease – United States, 2000. MMWR 2002;51:141-4.
Borrow et al. Safe laboratory handling of *Neisseria meningitidis.* J of Infection 2014; 68:305-312.

Microbiologists

- **Attack rate of 13/100,000 among microbiologists who work with *Neisseria meningitidis*[1]**
  - High case fatality ratio, possibly due to exposure to high concentration of organisms and highly virulent strains
  - Majority of cases occurred in clinical microbiologists who were not using respiratory protection at the time of exposure

[1]Cohn et al. Prevention and Control of Meningococcal Disease. MMWR. March 22, 2013; 62 (RR-2)

Outbreaks of Meningococcal Disease

- **Meningococcal outbreaks are rare, historically causing ~2–3% of US cases[1]**
- **Five serogroup B meningococcal disease clusters/outbreaks on college campuses during 2009–2013**
  - 200-1400 fold increased risk in students during outbreak period
- **Threshold for vaccination for serogroup B outbreaks under a MenB IND in institutional settings[2]**
  - 2 cases in population <5,000 persons
  - 3 cases in population ≥5,000 persons

[1] National Notifiable Diseases Surveillance System
[2] http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf

Recent Experience With Serogroup B Meningococcal Disease on College Campuses

- Two outbreaks of serogroup B meningococcal disease on college campuses in 2015
- Additional sporadic cases of serogroup B meningococcal disease in college students have been reported to CDC

How Many People Fall Into Each Risk Group?

Group	Estimated persons aged ≥10 years	Reported cases
Persistent complement component deficiencies	Prevalence of 0.03% ~80,000 persons	6 cases since 2005 in ABCs[1] (none serogroup B)
Anatomic or Functional Asplenia (including sickle cell)	Sickle cell ~90,000-100,000 (all ages)[3]	11 cases since 1995 in ABCs[1] (2 serogroup B)
Microbiologists	~100,000 clinical; 400 research	22 cases worldwide 1985-2014[2,3] (at least 10 serogroup B)
Outbreak at-risk populations	60,000 in 5 serogroup B university outbreaks	32 cases combined 2009-2013[4]
Total	300,000-350,000 persons	

[1]Active Bacterial Core surveillance (ABCs)

[2]Sejvar et al. Assessing the risk of laboratory acquired meningococcal disease. J Clin Microbiol 2005; 43:4811-4.
CDC. Laboratory-acquired meningococcal disease – United States, 2000. MMWR 2002;51:141-4.
[3]Borrow et al. Safe laboratory handling of *Neisseria meningitidis.* J of Infection 2014; 68:305-312.
[4]Reports to CDC, unpublished data

Special Populations Not Included for MenB

- **First-year college students living in residence halls**
  - Broader adolescent/college student policy options being considered separately
- **Travelers**
  - Risk primarily due to serogroups other than B
- **Military recruits**
  - Current serogroup B epidemiology similar to US population[1]
  - DOD sets own vaccination policy

1Broderick M, et al. Incidence of Meningococcal Disease in the United States Military Before and After Adoption of the Conjugate Vaccine (MCV-4). EID. Feb 2015.

SUMMARY OF VACCINE IMMUNOGENICITY AND SAFETY

Immunogenicity Summary

- **Demonstrated immune response in general adolescent population**
  - 86.1%-98.9% achieved protective antibody titers after 3 doses of Trumenba® [US adolescents and young adults]
  - 99%-100% for achieved protective antibody titers after 2 doses of Bexsero® [Chilean and UK adolescents and young adults]
    - 73%-93% [US and Polish adolescents and young adults]
  - Data not directly comparable for Trumenba® and Bexsero®
- **Immunogenicity data not currently available in groups at increased risk**
- **Limited short-term (18-23 months) antibody persistence data available for Bexsero®**

Additional Data to Inform Policy Decisions

- **Immunogenicity against additional strains to evaluate breadth of coverage**
- **Antibody persistence data**
- **Safety and immunogenicity data**
  - Concomitant vaccination (new data available for Trumenba®)
  - Groups at increased risk
  - Other age groups
- **Additional safety data** (new data available for Trumenba®)

Summary of Newly Available Data for Trumenba®

- **Safety and immunogenicity with concomitant administration of Trumenba® with Menactra® and Adacel®**
  - Local and systemic reactogenicity profile was similar when administered alone or concomitantly
  - Noninferior immune responses to all Tdap and MenACWY antigens, and MenB test strains
- **Safety and tolerability of Trumenba®**
  - Safety profile was consistent with studies that supported licensure

Personal communication, Laura York, Pfizer Vaccines

Timeline for Immunogenicity Data Specific to Populations at Increased Risk

- **Complement deficient and asplenic persons**
  - Data anticipated in 2016: 150 persons 2–17 years with 2 doses of Bexsero®
- **Laboratory workers:**
  - Small studies ongoing for both Trumenba® and Bexsero®

Safety Summary

- **MenB vaccines are more reactogenic than other vaccines given during adolescence**
- **Majority of local & systemic reactions are mild to moderate in severity and transient**
  - Most common AE was pain at injection site
- **SAE rare and similar between vaccine recipients and controls in clinical trials**
- **Safety data not currently available in groups at increased risk**

Other Sources of Safety Data for MenB Vaccines

- **Limited experience with MenB vaccines outside of clinical trials**
- **Bexsero®**
  - United States: approximately 17,000 persons vaccinated under an expanded access IND program for outbreak response at two universities
  - Canada: over 40,000 persons vaccinated in a regional public health program in Quebec (persons 2 months–20 years)
  - No concerning patterns among the adverse events observed
- **Trumenba®**
  - No post-licensure safety data yet

Additional Vaccine Safety Considerations

- **Theoretical concern from mouse models about autoimmune disorders following MenB vaccination[1,2]**
  - FDA reviewed these data and did not observe differences in rates of autoimmune disorders between vaccine recipients and controls in safety studies
- **Postlicensure safety surveillance will be conducted to detect any potential safety signals**
  - Will require a large number of doses administered to detect a potential safety signal in VSD
  - VAERS for passive surveillance

[1]Costa I, et al. Human Factor H (FH) Impairs Protective Meningococcal Anti-FHbp Antibody Responses and the Antibodies Enhance FH Binding. mBio. September/October 2014; 5(5): e10625-14.

[2]Granoff D. Improving Safety and Efficacy of Meningococcal Vaccines. 2014. Microbe. 9(8):321-327.

GRADE OUTCOMES

Initial Study Questions

Questions	Population
1. Should MenB vaccine be administered routinely to all adolescents and young adults?	Adolescents and young adults 10 through 25 years of age
2. Should MenB vaccine be administered to college students to prevent outbreaks?	College students 15 through 25 years of age
3. Should MenB vaccine be administered to persons at increased risk for serogroup B meningococcal disease?	Microbiologists, persons with persistent complement component deficiencies or functional or anatomic asplenia (including sickle cell anemia)
4. Should MenB vaccine be administered during outbreaks?	Individuals at increased risk for serogroup B disease because of an outbreak

Overview of Critical Outcomes by Question

Assessment	Outcome	Persons at increased risk	During outbreaks
Modified assessment of disease burden data	Burden of disease	X	
	Mortality of disease	X	X
	Long-term sequelae	X	X
	Serogroup B strain coverage	X	X
Quality of evidence assessed using standard GRADE approach	Short-term immunogenicity	X	X
	Persistence of immunogenicity (1-2 years after vaccination)	X	
	Serious adverse events	X	X

GRADE Criteria

- Risk of bias (methodological limitations)
- Inconsistency
- Indirectness
- Imprecision
- Publication bias
- Other considerations (strength of association, dose gradient, direction of all plausible residual confounding)

Evidence of Outcomes: Bexsero® (4CMenB)

	Outcome	Evidence Type (# of studies) for 4CMenB
Benefits	Short-term immunogenicity 1 month after 2 dose series	RCT(3) Open label (2)
	Persistence of immunogenicity 1-2 years after 2 dose series	RCT(2)
Harms	Serious adverse events	RCT(3)

- 6 studies in total: 2 open label studies and 4 RCTs
- 4 papers published
- 3 post vaccination campaign data

Evidence of Outcomes: Trumenba® (rLP2086)

	Outcome	Evidence Type (# of studies) for rLP2086
Benefits	Short-term immunogenicity 1 month after 3-dose series	RCT(2) Open label (3)
	Persistence of immunogenicity	None
Harms	Serious adverse events	RCT(5)

- 9 studies in total: 3 open label studies and 6 RCTs
- 3 papers published

Considerations for Vaccine Use: Bexsero® and Trumenba ®

Evidence type for benefits and harms	Bexsero®	Trumenba®
4CMenB/rLP2086 Use among persons at increased risk	Benefits: Evidence Type: 3 Harms: Evidence Type: 3 **Overall Evidence Type: 3**	Benefits: Evidence Type: 3 Harms: Evidence Type: 3 **Overall Evidence Type: 3**
4CMenB/rLP2086 Use during outbreaks	Benefits: Evidence Type: 2 Harms: Evidence Type: 2 **Overall Evidence Type: 2**	Benefits: Evidence Type: 2 Harms: Evidence Type: 2 **Overall Evidence Type: 2**

Working Group Rationale for Proposed Policy Option for Persons at Increased Risk

- Demonstrated disease risk in specific risk-groups
- Currently recommended vaccination with MenACWY
- Demonstrated immune response in general adolescent population
- No theoretical safety concerns in persons aged >25 years from vaccination compared to persons aged 10–25 years

Harmonization of MenB and MenACWY Recommendations for Groups at Increased Risk

- **MenACWY recommendations will be aligned with proposed MenB language**
  - Include eculizumab (Soliris®) as an indication for vaccination
  - Align wording for use in outbreaks with proposed wording for MenB
    - Persons identified to be at increased risk because of a meningococcal disease outbreak attributable to serogroup A, C, W, or Y
- **Differences: certain special populations (travelers, first year college students living in residence halls, and military recruits) not included in proposed MenB language**

Proposed Policy Option Language: MenB Vaccine for Persons at Increased Risk

- **A serogroup B meningococcal (MenB) vaccine series should be administered to persons aged ≥10 years at increased risk for meningococcal disease. (Category A) This includes:**
  - Persons with persistent complement component deficiencies[1]
  - Persons with anatomic or functional asplenia[2]
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)

[2]Including sickle cell disease

Guidance for Use

- Depending on the MenB product used, a compete 2 or 3 dose series of vaccine is required for protection from serogroup B meningococcal disease
- The same vaccine product should be used for all doses
- No product preference to be stated

Work Group Members

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Thank You

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Vote

- **A serogroup B meningococcal (MenB) vaccine series should be administered to persons aged ≥10 years at increased risk for meningococcal disease. (Category A) This includes:**
  - Persons with persistent complement component deficiencies[1]
  - Persons with anatomic or functional asplenia[2]
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)

[2]Including sickle cell disease