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

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Advisory Committee on Immunization Practices
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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

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\(^1\)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\(^2\)

\(^2\)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

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
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?

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

\(^1\)Active Bacterial Core surveillance (ABCs)


\(^4\)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
  - DOD sets own vaccination policy

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

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## Initial Study Questions

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

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

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Evidence Type (# of studies) for 4CMenB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term immunogenicity</td>
<td>1 month after 2 dose series</td>
<td>RCT(3)</td>
</tr>
<tr>
<td>Persistence of immunogenicity</td>
<td>1-2 years after 2 dose series</td>
<td>RCT(2)</td>
</tr>
<tr>
<td>Harms</td>
<td>Serious adverse events</td>
<td>RCT(3)</td>
</tr>
</tbody>
</table>

- 6 studies in total: 2 open label studies and 4 RCTs
- 4 papers published
- 3 post vaccination campaign data
## Evidence of Outcomes: Trumenba® (rLP2086)

<table>
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<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Evidence Type (# of studies) for rLP2086</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term immunogenicity</td>
<td>1 month after 3-dose series</td>
<td>RCT(2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open label (3)</td>
</tr>
<tr>
<td>Persistence of immunogenicity</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Harms</td>
<td>Serious adverse events</td>
<td>RCT(5)</td>
</tr>
</tbody>
</table>

- 9 studies in total: 3 open label studies and 6 RCTs
- 3 papers published
## Considerations for Vaccine Use: Bexsero® and Trumenba®

<table>
<thead>
<tr>
<th>Evidence type for benefits and harms</th>
<th>Bexsero®</th>
<th>Trumenba®</th>
</tr>
</thead>
<tbody>
<tr>
<td>4CMenB/rLP2086 Use among persons at increased risk</td>
<td>Benefits: Evidence Type: 3 Harms: Evidence Type: 3 <strong>Overall Evidence Type: 3</strong></td>
<td>Benefits: Evidence Type: 3 Harms: Evidence Type: 3 <strong>Overall Evidence Type: 3</strong></td>
</tr>
<tr>
<td>4CMenB/rLP2086 Use during outbreaks</td>
<td>Benefits: Evidence Type: 2 Harms: Evidence Type: 2 <strong>Overall Evidence Type: 2</strong></td>
<td>Benefits: Evidence Type: 2 Harms: Evidence Type: 2 <strong>Overall Evidence Type: 2</strong></td>
</tr>
</tbody>
</table>
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 complete 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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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
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
- Persons with anatomic or functional asplenia
- Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
- Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

1Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)
2Including sickle cell disease