Considerations for Serogroup B Meningococcal (MenB) Vaccine Booster Doses in Persons at Increased Risk for Serogroup B Meningococcal Disease

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Advisory Committee on Immunization Practices
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Timeline of ACIP Recommendations for Groups at Increased Risk of Meningococcal Disease

MPSV4 polysaccharide vaccine recommended for groups at increased risk

~1980

MenACWY conjugate vaccine recommended for persons 11–55 years at increased risk
- Original age indication for licensure
- Recommended for children 2–10 years and infants as licensed indication expanded
- MPSV4 was available for other age groups

2005

Booster doses of MenACWY conjugate vaccine added for certain groups who remain at increased risk

2010
MenACWY Conjugate Vaccine Booster Recommendations

- Rationale for MenACWY booster recommendations:
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease
  - Evidence of waning functional antibody 3–5 years after a single dose of MenACWY
  - Evidence of booster response to revaccination
  - Low-risk for serious adverse events
  - Accepted standard of care for high-risk groups

- Booster doses of MenACWY recommended every 5 years* throughout life for certain persons who remain at increased risk for meningococcal disease

*If most recent dose received before age 7 years, a booster dose should be administered 3 years later.
Two Serogroup B Meningococcal (MenB) Vaccines Licensed for Persons Aged 10–25 Years in 2014 and 2015

- MenB-FHbp (Trumenba®, Pfizer)
  - Two components (fHbp subfamily A/v2,3; subfamily B/v1)
  - 3-dose series, administered at 0, 1–2, and 6 months
    - Persons at increased risk for serogroup B meningococcal disease
  - 2-dose series, administered at 0 and 6 months
    - Healthy adolescents who are not at increased risk for meningococcal disease

- MenB-4C (Bexsero®, GlaxoSmithKline)
  - Four components (fHbp subfamily B/v1; NhbA; NadA; Por A1.4)
  - 2 dose series, administered at 0 and ≥1 month
  - Licensed in >35 countries for persons ≥2 months of age
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2010

MenB vaccine recommended for persons ≥10 years at increased risk

2015
Current ACIP MenB Vaccine Recommendations

- Certain persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine (Category A); February 2015:
  - Persons with persistent complement component deficiencies
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis*
  - Persons identified as at increased risk because of a serogroup B meningococcal disease outbreak

- Adolescents and young adults aged 16–23 years may receive MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease (Category B); June 2015

- No ACIP guidance for booster doses to date

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

- Certain persons at increased risk for meningococcal disease likely remain at increased risk throughout their lifetime
- Data suggest waning of antibodies after vaccination with MenB vaccines
- Limited data on:
  - Immunogenicity of MenB primary series among immunocompromised subjects
  - Duration of protection of MenB vaccines among persons at increased risk
  - Efficacy of MenB booster doses among persons at increased risk
- Unlikely more data will become available for persons at increased risk
- Need to optimize protection for persons at increased risk for meningococcal disease
Outline

- Review of groups at increased risk for serogroup B meningococcal disease
- Immunogenicity of MenB-4C (Bexsero®) among immunocompromised subjects
- Antibody persistence and response to booster dose following primary series of MenB-FHbp (Trumenba®) or MenB-4C (Bexsero®) among healthy subjects
- Proposed policy option
Persons at Increased Risk for Serogroup B 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)
  - Up to 10,000-fold increased risk and can experience recurrent disease
  - Prevalence of ~0.03% in general population (all complement component deficiencies)\(^1\)

- Complement component deficiencies are often recognized as a result of a meningococcal infection
  - Frequency of complement component deficiency among individuals with meningococcal disease in the U.S. estimated between 7%–25%\(^2\)

Eculizumab (Soliris®)

- Monoclonal antibody indicated 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
- 16 cases of meningococcal infection (1 death) out of 5207 person-years of eculizumab exposure during 2007–2014
  - 2000 times the occurrence of meningococcal disease among U.S. population
  - 1 serogroup B, 2 serogroup C, 2 serogroup Y, 11 unknown serogroup
  - All vaccinated with MenACWY
- Recent MenB vaccine failure identified among patient taking eculizumab in UK
- The number of patients taking eculizumab is unknown
  - aHUS and PNH are rare conditions (~300 persons with aHUS and ~10,000 with PNH in U.S.)

3. [Website](http://atypicalhus.ning.com/page/what-is-ahus)
4. [Website](http://imgjp1.pnhsource.jp/Downloads/pdf/UnderstandingPNHBrochure.pdf)
Persons with Functional or Anatomic Asplenia

- Asplenic persons are at increased risk for invasive infection caused by many encapsulated bacteria, including *Neisseria meningitidis*.
- Includes sickle cell disease which affects ~100,000 persons of all ages\(^1\).
- Higher case-fatality ratio (40%-70%)\(^2\)
  - Compared to 10-20% case-fatality ratio among U.S. population\(^3\).
- Demonstrated significantly lower response to 1 dose of MenC vaccine\(^4\).

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\(^1\)www.cdc.gov/ncbddd/sicklecell/data.html  
\(^2\)MMWR. January 28, 2011; 60(3): 72-76.  
\(^3\)Cohn AC. Clin Infect Dis 2010;50:184-91  
\(^4\)Balmer P. Infection and Immunity, Jan 2004, 332-337
Microbiologists

- Attack rate of 13/100,000 among U.S. microbiologists who work with *Neisseria meningitidis*¹
  - Compared to rate of 0.1–0.2/100,000 among U.S. population
  - High case fatality ratio, possibly due to exposure to high concentrations of organisms and highly virulent strains
  - Majority of cases occurred in clinical microbiologists who were not using respiratory protection at the time of exposure

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 2008–2014
  - 200–1400 fold increased risk in students during outbreak period
- Six additional serogroup B meningococcal disease clusters/outbreaks on college campuses during 2015–2016

\(^1\) National Notifiable Diseases Surveillance System
Active Bacterial Core surveillance (ABCs)

- Active laboratory- and population-based surveillance in 10 states
  - Covers 43 million persons, ~13% of U.S. population

- Collects information in the medical record for meningococcal disease cases with:
  - Anatomic/functional asplenia and sickle cell disease (since 1995)
  - Complement component deficiencies (since 2005)
    - Limitation: information on diagnosis of complement component deficiencies may not be available until after hospitalization for meningococcal disease and therefore may not be captured in ABCs
### How Many People Fall into Each Risk Group?

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimated Persons in Risk Group</th>
<th>Reported Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement component deficiencies</td>
<td>Prevalence of 0.03%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6 cases since 2005 in ABCs&lt;sup&gt;1&lt;/sup&gt; (none serogroup B)</td>
</tr>
<tr>
<td></td>
<td>~70,000 persons (adults)</td>
<td></td>
</tr>
<tr>
<td>Anatomic or Functional Asplenia</td>
<td>Sickle cell</td>
<td>13 cases since 1995 in ABCs&lt;sup&gt;1&lt;/sup&gt; (3 serogroup B)</td>
</tr>
<tr>
<td>(including sickle cell)</td>
<td>~100,000 (all ages)&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Microbiologists</td>
<td>~100,000 clinical; 400 research</td>
<td>22 cases worldwide 1985-2014 (at least 10 serogroup B)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~270,000 persons</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Active Bacterial Core surveillance (ABCs)


<sup>3</sup>www.cdc.gov/ncbddd/sicklecell/data.html

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<th>Group</th>
<th>Estimated Persons in Risk Group(^1)</th>
<th>Reported Cases(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreak at-risk populations (2008–2016)</td>
<td>~180,000 students identified as at risk during 11 serogroup B university outbreaks</td>
<td>50 cases (3 deaths) (2008–2016)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~20,000 students per year or ~16,000 students per outbreak</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Outbreaks where CDC was consulted
Summary: Persons at Increased Risk for Serogroup B Meningococcal Disease

- Persons at increased risk for serogroup B meningococcal disease represent
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease

- For persons with complement component deficiencies, anatomic/functional asplenia, and most microbiologists increased risk is ongoing

- For persons at increased risk because of serogroup B meningococcal disease outbreak the risk period may be more limited
Immunogenicity of MenB-4C (Bexsero®) among Immunocompromised Subjects
MenB-4C (Bexsero®): Safety, Tolerability, and Immunogenicity of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

Data courtesy of Glaxo Smith Kline
MenB-4C (Bexsero®): Immunogenicity (hSBA ≥1:5 Using Exogenous Complement*) of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

*Complement derived from healthy adult sera added during the hSBA assay
MenB-4C (Bexsero®): Immunogenicity (hSBA ≥1:4 with Endogenous Complement*) of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

*Source of complement for the hSBA assay is the test serum itself
MenB-4C (Bexsero®): Immunogenicity (hSBA ≥1:4 Using Endogenous Complement*) of Two Doses When Administered to Immunocompromised Subjects Aged 2–17 Years at Increased Risk of Meningococcal Disease

*Source of complement for the hSBA assay is the test serum itself
Summary: Immunogenicity of MenB-4C (Bexsero®) among Immunocompromised Subjects

- Increase in hSBA response observed in subjects aged 2–17 years with complement component deficiency and asplenia and in subjects receiving eculizumab after two doses of MenB-4C (Bexsero®)
  - Comparable responses were observed in healthy subjects and subjects with asplenia
  - Lower responses were reported in subjects with complement component deficiencies, especially if endogenous complement was used in the hSBA assay
  - Subjects receiving eculizumab showed an increase in hSBA titers, but had the lowest response
Antibody Persistence and Response to Booster Dose among Healthy Subjects
<table>
<thead>
<tr>
<th>Population</th>
<th>Antibody persistence</th>
<th>Booster response</th>
<th>Antibody persistence</th>
<th>Booster response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents (11–17 or 11–18 years old)</td>
<td>up to 48 months</td>
<td>at 48 months</td>
<td>up to 11–24 months</td>
<td>-</td>
</tr>
<tr>
<td>Children (4–7 and 8–12 years old)</td>
<td>-</td>
<td>-</td>
<td>up to 24–36 months</td>
<td>at 24–36 months</td>
</tr>
</tbody>
</table>
MenB-FHbp (Trumenba®): Antibody Persistence (hSBA ≥1:4) up to 48 Months in European Adolescents Aged 11–18 Years following Completion of 2-Dose (0, 6 m) and 3-Dose (0, 2, 6 m) Primary Series
MenB-FHbp (Trumenba®): Antibody Persistence (hSBA ≥1:4) up to 48 Months in European Adolescents Aged 11–18 Years following Completion of 2-Dose (0, 6 m) and 3-Dose (0, 2, 6 m) Primary Series and hSBA Responses to a Booster Dose at 48 Months Post Primary Series
MenB-4C (Bexsero®): Antibody Persistence (hSBA ≥1:4 or ≥1:5) up to 11–24 Months following Completion of 2-Dose Primary Series in Adolescents

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Percentage of subjects with protective titers* 1 month after series completion</th>
<th>Percentage of subjects with protective titers after time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fHbp</td>
<td>NadA</td>
</tr>
<tr>
<td>11 months¹ (U.K.)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>18–24 months² (Chile)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

MenB-4C (Bexsero®): Antibody Persistence (hSBA ≥1:4) at 24–36 Months Post Primary Series and hSBA Responses to a Booster Dose at 24–36 Months Post Primary Series in Children Aged 4–7 and 8–12 Years*

Data courtesy of Glaxo Smith Kline; study countries Spain and Hungary
Anticipated Studies

- 4 year antibody persistence and booster response among adolescents from Canada and Australia after completion of primary series of MenB-4C (Bexsero®)
  - Anticipate by Q2 2017
Safety Summary

- MenB vaccines are more reactogenic than other vaccines given during adolescence
  - Most common adverse event reported is pain at injection site
- The safety and tolerability profiles are similar for the primary series and one additional booster dose
Summary: MenB Vaccine Antibody Persistence and Booster Response Among Healthy Subjects

- Evidence of waning antibody for both MenB vaccines
  - As early as 12 months after completion of the primary series
  - Different waning rates observed to each antigen/strain
- Data from two MenB vaccines not directly comparable
- Evidence of booster response to revaccination
- Low-risk for serious adverse events
Work Group Interpretation
Work Group Interpretation

- Persons at increased risk for serogroup B meningococcal disease represent small targeted groups with a demonstrated increased risk for meningococcal disease
- MenB vaccines are immunogenic in persons at increased risk for meningococcal disease
- Waning of antibody observed as early as 12 months post-vaccination
- Booster response observed in previously vaccinated subjects following one additional MenB dose
Working Group Rationale

- Rationale for MenB booster doses:
  - Small targeted groups
  - Demonstrated increased risk for meningococcal disease
  - Evidence of waning antibody as early as 12 months after MenB vaccination
  - Evidence of booster response to revaccination
  - Low-risk for serious adverse events
  - Accepted standard of care for high-risk groups
Timing of Booster Doses

- The Work Group discussed the appropriate timing/interval for MenB booster doses extensively
  - Persons who remain at increased risk for serogroup B meningococcal disease (i.e., persons with complement component deficiencies, asplenia, and microbiologists)
  - In outbreak settings
- Desire to harmonize timing of booster recommendations with MenACWY for persons who remain at increased risk
  - To improve compliance with booster doses of both vaccines
  - Ensure some level of protection is maintained over time in these higher-risk individuals
  - Recognition that there is evidence of waning antibody as early as 12 months after MenB vaccination
- In outbreak settings, where the period of increased risk is more limited, a booster dose at a shorter interval (i.e., ≥6-12 months) may help to ensure antibody is maximized during the outbreak period
Consensus of Work Group

- The Meningococcal Work Group supports routine MenB booster doses for persons at increased risk of serogroup B meningococcal disease

- Harmonize timing of booster doses with MenACWY boosters for groups at prolonged increased risk for meningococcal disease

- In outbreak settings, booster doses should be administered if it has been ≥6 months since their last MenB dose
Policy Option

- Booster doses of MenB vaccine should be administered every 5 years throughout life to persons aged ≥10 years in each of the following groups:
  - Persons with persistent complement component deficiencies including persons taking eculizumab
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of *Neisseria meningitidis* (as long as exposure continues)

- Booster doses of MenB vaccine should be administered to persons identified as at increased risk because of a serogroup B meningococcal disease outbreak if it has been ≥6 months since their last MenB dose
  - When multi-year or prolonged outbreaks occur, CDC should be consulted and recommendations for additional booster doses will be considered on a case-by-case basis
Next Steps: June 2017 ACIP Meeting

- GRADE evaluation of data supporting MenB booster doses
- An ACIP vote on routine MenB booster doses in persons aged ≥10 at increased risk for serogroup B meningococcal disease will be proposed at the June 2017 ACIP meeting
Discussion

- Are there additional data that ACIP would like to review?
- Does ACIP agree with the proposed policy option language and timing for booster doses in persons with complement component deficiencies, asplenia, and microbiologists?
- Does ACIP agree with the proposed policy option language and timing for booster doses in outbreak settings?
  - For persons previously vaccinated who later are in an outbreak?
  - For persons within a prolonged outbreak scenario?
For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.