MENINGOCOCCAL EPIDEMIOLOGY AND VACCINE RECOMMENDATIONS IN THE UNITED STATES

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Disclosures

Donna Curtis:

• Sanofi-Pasteur provides influenza vaccine and will run one serum test for an investigator-initiated study for which I am the PI.
• No other relevant disclosures
Objectives

• Describe the epidemiology of meningococcal disease in the United States.

• Describe current CDC vaccine recommendations for meningococcal disease, including recommendations for recently licensed meningococcal-B vaccines.
Outline

• Meningococcal Epidemiology

• Vaccine recommendations
  – CDC recommended vaccine schedule for A, C, W, Y serogroups
  – Group B vaccines
    • Why they are different
    • Review of safety and immunogenicity of licensed serogroup B meningococcal vaccines
    • ACIP/CDC recommendations for MenB vaccines
Meningococcal Disease and Epidemiology
Neisseria meningitidis

• Gram-negative, aerobic diplococcus polysaccharide capsule
• 5 serogroups cause most disease worldwide – A, B, C, W, and Y
  – B, C, Y cause most disease in the US
• Carried asymptotically in the nasopharynx of 1 in 10 people
  – Carriage can be as high as 30% in high-risk groups such as adolescents

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Primarily Sub-Saharan Africa; uncommon in the Americas and Europe</td>
</tr>
<tr>
<td>B</td>
<td>Causes ~50% of US infant disease; Causes substantial percentage of cases in US, Australia, and Europe;</td>
</tr>
<tr>
<td>C</td>
<td>Causes a substantial percentage of cases in the US, Australia, and Europe; associated with community and school based outbreaks</td>
</tr>
<tr>
<td>W-135</td>
<td>Uncommon worldwide; Outbreaks associated with Hajj pilgrimage, Africa</td>
</tr>
<tr>
<td>X</td>
<td>Cause of outbreaks in Sub-Saharan Africa; no vaccine available</td>
</tr>
<tr>
<td>Y</td>
<td>Causes a substantial percent of cases in the US and other countries in the Americas</td>
</tr>
</tbody>
</table>
Global distribution of meningococcal disease by serogroup, www.meningitisinfo.com
Neisseria meningitidis transmission and epidemiology

- Transmitted person-to-person:
  - via sharing/exchange of respiratory or throat secretions during close or lengthy contact

- Most cases are sporadic
  - <5% being associated with an outbreak

- Household members have 500-800 times the rate of disease as the general population
Neisseria meningitidis: Risk factors for invasive disease

• Host factors:
  – Terminal complement pathway deficiency
  – Asplenia
  – Age – infants, adolescents and young adults, adults >65 years at highest risk

• Environmental factors:
  – Contacts:
    • Outbreaks
    • Household or close contact exposure
    • Crowding (Hajj)
    • Travel (meningitis belt in Africa)
  – Concurrent upper respiratory tract infection; smoking (active/passive)
Why increased incidence of meningococcal disease in adolescence and young adulthood?

- Increased person to person transmission due to crowded living conditions and behaviors
  - Living in dormitories
  - Going to bars and parties
  - More than one kissing partner
  - Sharing cups, beverages
  - Sports teams
  - Smoking
Carriage Rate Of Meningococcus in College Students

- Day 1: 10%
- Day 2: 15%
- Day 3: 20%
- Day 4: 25%
- Oct: 30%
- Nov: 35%
- Dec: 35%

Pathophysiology of invasive disease

Organism Enters Nasopharynx

Colonization established

Specific bactericidal antibody present?

Yes

No Disease

Yes

Development of Antibody = No disease

No

Organism gains access to vascular space = Disease
Meningococcal disease

- With the success of vaccination against *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* are now the leading causes of bacterial meningitis in the U.S
  - ≥50% of meningococcal disease presents as meningitis
  - ~20% presents as sepsis (meningococcemia)
- Also causes:
  - pneumonia, arthritis, and rarely other localized infections
- Case fatality rate for invasive disease: 10-15%
Infants <1 Year of Age Show Highest Estimated Incidence 5.38: United States, 1998-2007

Figure 13. Estimated Incidence of Meningococcal Disease in Infants, Adolescents and Adults: United States, 1998-2007

Figure 16. Case-fatality rate for meningococcal disease in the United States by age group, 1998–2007
### Estimated Average Annual Cases, Deaths, and Sequelae by Age Group and Serogroup, 2009–2013

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases(^1)</th>
<th>Deaths(^2)</th>
<th>Sequelae(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serogroup B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>74–94</td>
<td>7-14</td>
<td>7-19</td>
</tr>
<tr>
<td>11-24 years</td>
<td>54–67</td>
<td>5-10</td>
<td>5-13</td>
</tr>
<tr>
<td>All ages</td>
<td>203–260</td>
<td>20-39</td>
<td>20-52</td>
</tr>
<tr>
<td>Serogroups C &amp; Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>34–43</td>
<td>3-6</td>
<td>3-9</td>
</tr>
<tr>
<td>11-24 years</td>
<td>62–77</td>
<td>6-12</td>
<td>6-15</td>
</tr>
<tr>
<td>All ages</td>
<td>307–393</td>
<td>31-59</td>
<td>31-79</td>
</tr>
</tbody>
</table>

- The majority (~80%) of serogroup B cases that occur in 11–24 year olds occur in older adolescents and young adults aged 16–24 years.

\(^1\)Range in estimated cases: Low=NNDS data supplemented with additional serogroup data from ABCs and state health departments, High= NNDS data supplemented with additional serogroup data from ABCs and state health departments + proportion serogroup B or serogroup C & Y applied to cases with unknown serogroup.

\(^2\)10-15% case fatality ratio

\(^3\)10-20% cases with long term sequelae
Meningococcal disease sequelae, US

Figure 14. Sequelae among patients from 10 children’s hospitals who contracted meningococcal disease, United States, 2001–2005.4

- Amputation: 1.4%
- Hemiplegia: 2.1%
- Ataxia: 2.8%
- Seizures: 6.2%
- Skin necrosis: 9.6%
- Hearing loss: 9.6%

Meningococcal Disease Incidence, United States, 1970-2013

Meningococcal Incidence and Vaccine Coverage, 1993-2013

Meningococcal Incidence in All Ages by Serogroup and Adolescent MenACWY Vaccine Coverage, 1993-2013

2013: 564 cases (0.18/100,000)^3

Incidence per 100,000

Source: ABCs cases from 1993-2013 estimated to the U.S. population with 18% correction for under reporting

National Immunization Survey – Teen; 2006-2013

NNDSS 2013 final case count

McNeil J, CDC, ACIP Presentation, October 2014
Epidemiology of Serogroup B Meningococcal Disease

- With changing background epidemiology and widespread use of meningococcal ACWY conjugate vaccines (MenACWY) in adolescents and young adults
  - Serogroup B now causes 40% of all meningococcal disease cases in 11-24 year olds
  - Approximately 50-70% of cases of serogroup B disease in 18-23 year olds occur in college students
Meningococcal Incidence by Serogroup and Age-Group, United States, 2005-2013

SOURCE: CDC. National Notifiable Diseases Surveillance System with additional serogroup data from Active Bacterial Core surveillance and state health departments. Unknown serogroup (25%) and other serogroups (8%) excluded
DESCRIPTION OF THE OUTBREAK THAT PRECEDED LICENSURE OF MENB VACCINES
Princeton University Outbreak

- March 2013, Princeton student developed serogroup B meningococcal disease while on spring break with her family in another state
- Several weeks later, a prospective student developed serogroup B meningococcal disease—cases were not recognized as connected
- A few weeks later, a second Princeton student was diagnosed with mening B
- New Jersey Health Dept recognized there were 3 cases related to Princeton
  - Widespread education/hygiene campaign began at Princeton on ways to reduce transmission
Princeton Outbreak

- 4\textsuperscript{th} case was identified and genetic testing showed all isolates identical
  - Outbreak was declared
- End of the school year (2013) approaching
  - Estimated 20,000 people coming to campus for graduation activities and a reunion
  - No new cases at end of semester
- June 2013, 5\textsuperscript{th} case occurred in a Princeton student traveling with other students in Greece
Princeton Outbreak

- July 2013, Princeton and CDC discussed obtaining IND for meningococcal serogroup B vaccine (MenB) to interrupt outbreak
- Fall classes started
  - Hygiene and education campaign continued
  - 3 more cases occurred (#6-8)
- IND approved in late November, just prior to 8th case
  - Vaccine clinics organized—1st one occurred in early Dec; 2nd dose clinics started in Feb
  - By May 14, 2014, 94.9% of the target population had received at least 1 dose of the vaccine and 89.1% had received both doses
Princeton Outbreak

• March 2014 a Drexel University student died of invasive mening B (same strain) after contact with a group of students from Princeton who traveled to Drexel for a social event (#9)
  – Most of the Princeton students had received 2 doses of vaccine

• Princeton began offering serogroup B mening vaccine to incoming freshman in fall 2014

• No students receiving the 2 dose vaccine developed meningococcal disease

Addressing the Challenges of Serogroup B Meningococcal Disease Outbreaks on Campuses, NFID, May 2014; McNamara LA. Pediatrics 135(5);798-804, 2015
Use of Serogroup B Vaccine

McNamara LA. Pediatrics 135(5);798-804, 2015
Princeton Outbreak

- No cases in students receiving 1 or more doses of MenB suggests the vaccine was effective in protecting against disease in vaccinees

- 9th Case in the Drexel student after vaccine campaigns suggests
  - Strain was still circulating
  - Carriage not completely eliminated by vaccination
CDC Recommendations for A, C, Y, W Meningococcal Vaccines
## Licensed vaccines against A, C, W, Y

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Name</th>
<th>Serogroups included</th>
<th>Minimum age of approval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugate</td>
<td>MenACWY-D (Menactra)</td>
<td>A, C, W, Y</td>
<td>9 mos</td>
</tr>
<tr>
<td>Conjugate</td>
<td>MenACWY-CRM (Menveo)</td>
<td>A, C, W, Y</td>
<td>2 mos</td>
</tr>
<tr>
<td>Conjugate</td>
<td>Hib-MenCY (MenHibrix)</td>
<td>A, C + Hib</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Polysaccharide</td>
<td>MPSV4 (Menomune)</td>
<td>A, C, W, Y</td>
<td>2 years</td>
</tr>
</tbody>
</table>

* This is the youngest age for which the vaccine is approved. This age does not necessarily correlate with ACIP/CDC recommendations.
CDC vaccine recommendations for children

• Routine recommendations, quadrivalent conjugated vaccines (MCV4 = MenACWY-D or MenACWY-CRM):
  – One dose at 11-12 years
  – One dose at 16 years of age (booster)

• Special groups – refer to most updated CDC vaccine schedule for full details:
  – HIV-positive: give 2 doses as primary vaccine
  – Anatomic or functional asplenia
  – Children with persistent complement component deficiency includes:
    • persons with inherited or chronic deficiencies in C3, C5-9, properidin, factor D, factor H, or taking eculizumab (Soliriis®)
  – Travel to country where meningococcal disease is hyperendemic or epidemic (i.e. African meningitis belt or Hajj)
  – Community outbreaks with a vaccine serogroup
CDC vaccine recs for adults

High-risk adult groups:

- Complement component deficiency (same as kids)
- Functional or anatomic asplenia
- **Profession with routine exposure to Neisseria meningitidis**
- Traveling or residing in countries in which the disease is common
- At increased risk for a serogroup A, C, W or Y meningococcal disease outbreak
- **First-year college student living in a residence hall**
- **Military recruits**
CDC vaccine recs for adults

Vaccines:

- MCV4 should be used through age 55
- Only the polysaccharide vaccine (MPSV4, Menomune) is approved for adults ≥65 yrs
- Adults at increased risk because of complement component deficiencies and persons with functional or anatomic asplenia should receive a two-dose primary series 2 months apart and then get a booster dose every 5 years.
Serogroup B Meningococcal Vaccines
Challenges with Meningococcal Serogroup B Vaccines

• Polysialic acid is present in the polysaccharide capsule of Serogroup B
  – Antigenically similar to human neuronal tissue
  – Seen as a “self” antigen
  – Poorly immunogenic
  – Potential to induce autoimmune response

• Current vaccine development focuses on
  – Use of subcapsular antigens which are
    • Surface exposed
    • Conserved
    • Induce bactericidal activity
Outer Membrane Antigens

- Factor H Binding Proteins (FHbp)
  - Allows bacteria to evade complement mediated lysis
- NadA
  - Allows bacteria to adhere and invade epithelial cells
- Neisseria Heparin Binding Antigen (NHBA)
  - Promotes bacterial survival in the blood
- Outer membrane vesicles (OMV)
  - Buds from the cell membrane
  - Important in protein trafficking and secretion
  - Porin protein, PorA, elicits strong serum bactericidal antibody in children and adults
Figure 1
Meningococcal B Vaccines Approved in the U.S.

• MenB-FHbp (Trumenba, Pfizer) for ages 10-25 years
  – 3 dose series at 0, 2, 6 months
  – Component: factor H binding proteins, subfamily A/v2,3 and B/v1 (bivalent)
  –Licensed in US October 29, 2014

• MenB-4C (Bexsero, Novartis) for ages 10-25 years
  – 2 dose series at 0, ≥1 month
  – 4 component vaccine (-4C): fHbp subfamily B/v1, NhbA, NadA, PorA1.4
  – Licensed in >37 countries for persons ≥2 mos of age
Safety
## Licensed Meningococcal B Vaccines*

<table>
<thead>
<tr>
<th></th>
<th>MenB-4C (Bexsero)</th>
<th>MenB-FHbp (Trumenba)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indicated ages</strong></td>
<td>10-25 years</td>
<td>10-25 years</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>2 doses; 0, 1-6 mo</td>
<td>3 doses; 0, 2, 6 mo apart</td>
</tr>
<tr>
<td><strong>Most Common Reported Adverse Reactions after dose 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td>Erythema</td>
<td>50%</td>
<td>20%</td>
</tr>
<tr>
<td>Induration</td>
<td>32%</td>
<td>22%</td>
</tr>
<tr>
<td>Fever &gt;38°C</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>33%</td>
<td>55%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37%</td>
<td>62%</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>49%</td>
<td>42%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Package insert information for MenB-4C and MenB-FHbp, 2015*
Safety Data Outside Clinical Trials

• MenB-4C
  – 17,000 persons vaccinated under IND for University outbreaks
  – 40,000 vaccinated in Quebec in response to outbreak (2 mo-20 years of age)
  – >37 countries have licensed the vaccine

• MenB-FHBP
  – Safety data collected during recent outbreak responses at Providence college, University of Oregon
Safety Monitoring

- **Vaccine Adverse Event Reporting System (VAERS)**
  - Few reports received as of 10/05/2015
    - MenB-FHbp  n=65
    - MenB-4C    n=21
  - No safety signals detected to date

- **Vaccine Safety Datalink (VSD)**
  - Few doses administered in the VSD population to date
  - Safety assessment can begin when a larger number of doses have accumulated
MenB-4C: Evidence of Harms Post Vaccination Campaign SAEs Data

- 59,091 participants received at least one dose of MenB-4C
  - 60 SAEs were reported
    - 3 SAEs* determined to be related to the vaccine
    - 1 death** reported - unrelated to vaccine

* Rhabdomyolysis, anaphylaxis and fever
**Cause of death was drowning
MenB-FHbp: Evidence of Harms

- 11,338 participants received at least one dose of MenB-FHbp
  - 190 SAEs were reported in the vaccine group
    - 7 SAEs* determined to be related to vaccine
    - 1 death** reported - unrelated to vaccine

* Pyrexia, vomiting, vertigo, chills, headache, anaphylaxis and neutropenia
**Death due to road accident
Licensed MenB Vaccines-Safety

• Majority of local and systemic reactions are mild to moderate and transient
  – Pain at the injection site is the most common adverse event reported
  – Local reactions more common in adolescents than other vaccines used in this age group

• SAEs rare and similar to other vaccines
  – Anaphylaxis reported in 2 cases (1 each MenB-4C and 1 MenB-FHbp)
  – Low disease burden should be considered

• No concerning pattern of AEs yet identified

MacNeil J, ACIP meeting presentation, June 2015
Immunogenicity
Immunogenicity

• Studies starting in the late 1960s showing protection in infants from maternal antibody and then efficacy studies from the polysaccharide vaccine (MPSV4) have given us immune correlates of protection.

• For the FDA licensing endpoints, immunogenicity is measured by serum bactericidal antibodies as an immune correlate of protection against a small number of serogroup B strains.
  – Use a functional assay called serum bactericidal activity.
Immunogenicity

• Immunogenicity assessed by the
  – Proportion of subjects who achieved $\geq 4$ fold increase in hSBA titer for each strain tested and
    • hSBA indicates that human serum was used in the assay as a source of the complement
  – Proportion of subjects who achieved a titer $\geq$ LLOQ (lower limit of quantitation) of the assay for all strains (composite response)
Short-term immunogenicity

• MenB-4C (Bexsero)
  – At 1 mo following vaccination, composite response to 3 strains tested:
    • 90-94% of Chilean adolescents
    • 88% of university students in the UK (95% CI 82-93%)
    • 63% of adolescents in Australia and Canada

• MenB-FHbp (Trumenba)
  – At 1 mo following vaccination, composite response to 4 strains tested:
    • 81-83% of adolescents in the US
    • Similar results in European adolescents

Antibody Persistence Data

- **MenB-4C**
  - 11-mo follow-up (UK university students)
    - 66% had protective antibody after 2 doses (95% CI 58-72%)
  - 18-24 mo follow-up (Chilean adolescents)
    - 77%-94% had protective AB against the 3 antigens tested (fHBP, NAD, OMV) after 2 doses

- **MenB-FHbp**
  - 48 mo follow-up
    - >50% of vaccinees have hSBA and titers >LLOQ against 3 reference strains amongs adolescents in Australia, Spain and Poland

Concomitant Vaccine Administration

• 4MenB-4C (Bexsero)
  – Studies with concomitant vaccines in infants and children outside the US – no clinically significant interaction
  – No adolescent data

• MenB-FHbp (Trumenba)
  – 3 adolescent trials evaluating concomitant administration with HPV-4, MCV, Tdap, IPV
    • No immunologic interference with HPV 6,11,16, MenACWY, Tdap, IPV antigens observed
    • Possible decrease in HPV18
  – Reassuring for non-inferiority

CDC, MMWR Oct 23, 2015; Bhuyan P, ID Week; October 8–12, 2014; Philadelphia, PA; Vesikari T, Presented at 32nd ESPID, 2014; Dublin, Ireland.
### Potential cases and deaths prevented by different strategies for MenB vaccination of adolescents and young adults by age – United States

<table>
<thead>
<tr>
<th>Age at MenB series</th>
<th>Cases Prevented</th>
<th>Deaths Prevented</th>
<th>NNV to prevent case</th>
<th>NNV to prevent death</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 yrs</td>
<td>15</td>
<td>2</td>
<td>203,000</td>
<td>1,512,000</td>
</tr>
<tr>
<td>16 yrs</td>
<td>28</td>
<td>5</td>
<td>107,000</td>
<td>788,000</td>
</tr>
<tr>
<td>18 yrs</td>
<td>29</td>
<td>5</td>
<td>102,000</td>
<td>638,000</td>
</tr>
<tr>
<td>College student</td>
<td>9</td>
<td>1</td>
<td>368,000</td>
<td>2,297,000</td>
</tr>
</tbody>
</table>

**Abbreviations:** MenB = meningococcal B vaccine; NNV = number needed to vaccinate; QALY = quality-adjusted life years

What we know

• The vaccines appear safe and immunogenic.
• There is some effectiveness data from outbreak situations (Canada, Princeton)
• The vaccines received accelerated approval
  – Approval based on safety, immunogenicity
  – Serum bactericidal activity does have a correlate of protection
    • The serum bactericidal antibody (SBA) for licensure was done against representative strains of Serogroup B Neisseria meningitides

Rubin L, ACIP meeting presentation, Oct 21, 2015; CDC/ACIP
What is still unknown

• We do not know how effective the vaccines will be against all the circulating strains
  – Not all strains have the proteins in the vaccines
  – Variable expression of the proteins
  – Will they mutate?
• We do not know the duration of antibody persistence
  – Current data suggests it is short-term
• We do not know the impact on carriage
• We do not know the potential impact on circulating strains
• There are no studies comparing the two vaccines

Rubin L, ACIP meeting presentation, Oct 21, 2015; CDC/ACIP
ACIP recommendations for serogroup B meningococcal vaccines

• 2 Serogroup B meningococcal vaccines are licensed for persons 10-25 years of age

• Given the safety, immunogenicity and effectiveness data but also knowing the limitations of the data, recommendations are category B, permissive recommendations
  — Category A = for all persons in an age- or risk-factor group
  — Category B = for individual clinical decision-making
CDC recs on MenB vaccines

Clinical discretion:

• “Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) may be vaccinated with either a 2-dose series of Bexsero or a 3-dose series of Trumenba vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.”
CDC recs on MenB vaccines

For high-risk groups:

• “Persons 10 years or older who have not received a complete series. Administer a 2-dose series of Bexsero, at least 1 month apart. Or a 3-dose series of Trumenba, with the second dose at least 2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.”
QUESTIONS?