Epidemiology and Prevention of Meningococcal Disease in Adolescents

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July 16, 2015
Meningococcal Disease

- Three syndromes
  - Meningitis
  - Bloodstream infection
  - Pneumonia

- “Flu-like” symptoms early

- Rapidly progressive

- High morbidity and mortality
  - 10-15% case-fatality
  - 11-19% with long-term sequelae

- Most disease occurs in previously healthy persons
**Neisseria meningitidis** bacteria

**Capsule**
- 13 types
- 6 cause most disease globally (A, B, C, W, X, and Y)
- Target for conjugate vaccines

**Outer-membrane proteins**
- Targets for serogroup B vaccines
Nasopharyngeal Carriage

- Approximately 5-10% of the population are carriers
  - Adolescents and young adults have highest carriage rates
  - <1% of persons exposed who become carriers develop invasive disease

- Carriage is asymptomatic and ranges from weeks to months
  - Longer duration for strains that can establish long-term commensal relationships with the host
Meningococcal Disease Risk Factors

- **Pathogen Virulence Factors**
  - capsule, adhesins, nutrient acquisition factors, endotoxin release

- **Host Factors**
  - deficiencies in terminal complement pathway, asplenia, immunosuppression, genetic risk factors

- **Population/Environmental Factors**
  - household exposure, crowding, demographic and socio-economic factors, active and passive smoking, concurrent upper respiratory tract infections
EPIDEMIOLOGY AND BURDEN OF MENINGOCOCCAL DISEASE
Meningococcal Incidence in All Ages by Serogroup and Adolescent MenACWY Vaccine Coverage, 1993–2013

2013: 564 cases (0.18/100,000)

2013 MenACWY coverage, NIS-Teen:
- ≥1 dose: 77.8% (range by state, 40.4%-93.7%)
- 2 dose completion: 29.6%

1Source: Active Bacterial Core surveillance (ABCs) cases from 1993-2013 estimated to the U.S. population with 18% correction for nonculture confirmed cases. In 2010, estimated case counts from ABCs were lower than cases reported to the National Notifiable Diseases Surveillance System (NNDSS) and might not be representative.


3NNDSS 2013 final case count
Meningococcal Incidence by Serogroup* and Age-Group, 2005-2012

* NNDSS data with additional serogroup data from ABCs and state health departments. Unknown serogroup (23%) and other serogroups (8%) excluded.
Meningococcal Incidence in Adolescents and Young Adults by Serogroup, 2009–2013

Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments
Unknown serogroup (19%) and other serogroups (8%) excluded

1 Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments
Unknown serogroup (19%) and other serogroups (8%) excluded
Estimated Average Annual Cases by Age Group and Serogroup, 2009–2013

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serogroup B</td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>74–94</td>
</tr>
<tr>
<td>11-24 years</td>
<td>54–67</td>
</tr>
<tr>
<td>All ages</td>
<td>203–260</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serogroups C &amp; Y</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>34–43</td>
</tr>
<tr>
<td>11-24 years</td>
<td>62–77</td>
</tr>
<tr>
<td>All ages</td>
<td>307–393</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

¹Range in estimated cases: Low=NNDSS data supplemented with additional serogroup data from ABCs and state health departments. High= NNDSS 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.
## Average Annual Cases, Deaths, and Incidence from Serogroup B, 2009–2013

<table>
<thead>
<tr>
<th></th>
<th>Cases(^1)</th>
<th>Deaths(^1)</th>
<th>Incidence per 100,000(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 18–23 year olds</td>
<td>36</td>
<td>5</td>
<td>0.14</td>
</tr>
<tr>
<td>Estimated cases:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College students(^2)</td>
<td>14</td>
<td>2</td>
<td>0.09</td>
</tr>
<tr>
<td>Non-college students(^2)</td>
<td>22</td>
<td>3</td>
<td>0.21</td>
</tr>
</tbody>
</table>

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1. National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments
2. 40% of serogroup B cases in 18–23 year olds from ABCs were in college students (excluding unknown or missing), 2005–2013
3. Assume 61% of persons age 18–23 years enrolled in college
### Recent University Based Serogroup B Clusters/Outbreaks†

<table>
<thead>
<tr>
<th>University</th>
<th>Outbreak Period</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>University 1</td>
<td>Feb – Mar 2009</td>
<td>4</td>
</tr>
<tr>
<td>University 2</td>
<td>Nov 2011</td>
<td>2</td>
</tr>
<tr>
<td>University 3</td>
<td>Jan 2008 – Nov 2010</td>
<td>13</td>
</tr>
<tr>
<td>University 4</td>
<td>Mar 2013 – Mar 2014</td>
<td>9</td>
</tr>
<tr>
<td>University 5</td>
<td>Nov 2013</td>
<td>4*</td>
</tr>
<tr>
<td>University 6</td>
<td>Jan – Feb 2015</td>
<td>2</td>
</tr>
<tr>
<td>University 7</td>
<td>Jan – May 2015</td>
<td>7</td>
</tr>
</tbody>
</table>

†Where CDC consulted
*1 additional associated case identified after retrospective case review
Meningococcal Disease Case-Fatality Ratios by Serogroup and Age-group, 2005-2012

Case-fatality ratio:
All serogroups = 15.7%
Serogroups C & Y = 16.6%
Serogroup B = 12.5%

NNDSS data with additional outcome data from ABCs and state health departments. Unknown outcome excluded (18%)
MENINGOCOCCAL VACCINES
## Licensed Meningococcal Vaccine Products, U.S.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Manufacturer</th>
<th>Serogroups</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menactra®</td>
<td>Conjugate – Diphtheria toxoid</td>
<td>Sanofi Pasteur</td>
<td>A, C, W, Y</td>
<td>9 months—55 years</td>
</tr>
<tr>
<td>Menveo®</td>
<td>Conjugate - CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>Novartis Vaccines</td>
<td>A, C, W, Y</td>
<td>2 months—55 years</td>
</tr>
<tr>
<td>MenHibRix®</td>
<td>Conjugate – Tetanus toxoid</td>
<td>GSK Vaccines</td>
<td>C, Y</td>
<td>6 weeks—18 months</td>
</tr>
<tr>
<td>Menomune®</td>
<td>Polysaccharide</td>
<td>Sanofi Pasteur</td>
<td>A, C,W, Y</td>
<td>≥2 years</td>
</tr>
<tr>
<td>Trumenba®</td>
<td>Protein</td>
<td>Pfizer Vaccines</td>
<td>B</td>
<td>10—25 years</td>
</tr>
<tr>
<td>Bexsero®</td>
<td>Protein</td>
<td>Novartis Vaccines</td>
<td>B</td>
<td>10—25 years</td>
</tr>
</tbody>
</table>
Meningococcal Conjugate Vaccines

- **Benefits compared to polysaccharide vaccines**
  - Immunogenic in infants and young children
  - Superior immunologic memory with boosting on re-exposure
  - Prevent nasopharyngeal carriage with potential for herd immunity

- **Recent conjugate vaccine successes**
  - PCV, Hib vaccination programs in the United States
  - MenC conjugate vaccines in the United Kingdom
Current ACIP Meningococcal Conjugate Vaccine Recommendations

- **Routine vaccination of all adolescents aged 11-18 years**
  - 1st dose at age 11 or 12 years
  - Booster dose at age 16 years

- **Routine vaccination of persons aged ≥ 2 months at increased risk of meningococcal disease**
  - Vaccination of persons in at-risk groups to control outbreaks
Meningococcal Incidence in Adolescents and Young Adults by Serogroup, 2009–2013

Incidence per 100,000

Age (years)

Period of increased risk

Serogroup B

Serogroups C & Y

1Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

Unknown serogroup (19%) and other serogroups (8%) excluded
Coverage with ≥1 dose of Meningococcal Conjugate (MenACWY) among 13-17 year olds, NIS-Teen, 2006-2013

## Decreasing Incidence of Serogroup C, W, Y Meningococcal Disease in 11–19 Year Olds

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence per 100,000 (95% confidence intervals)&lt;sup&gt;1&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 year</td>
<td>11–19 years</td>
<td>≥20 years</td>
</tr>
<tr>
<td>2004-2005</td>
<td>0.77 (0.33, 1.55)</td>
<td>0.27 (0.17, 0.39)</td>
<td>0.17 (0.14, 0.21)</td>
</tr>
<tr>
<td>2006-2007</td>
<td>1.20 (0.61, 2.11)</td>
<td>0.31 (0.21, 0.45)</td>
<td>0.23 (0.19, 0.28)</td>
</tr>
<tr>
<td>2008-2009</td>
<td>0.93 (0.48, 1.69)</td>
<td>0.15 (0.08, 0.26)</td>
<td>0.23 (0.19, 0.27)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>1.37 (0.74, 2.33)</td>
<td>0.05 (0.02, 0.12)</td>
<td>0.14 (0.11, 0.18)</td>
</tr>
<tr>
<td>2012-2013</td>
<td>0.74 (0.39, 1.32)</td>
<td>0.05 (0.02, 0.10)</td>
<td>0.12 (0.10, 0.15)</td>
</tr>
</tbody>
</table>

- 80% decrease in serogroup C, W, Y meningococcal disease among 11–19 year olds

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<sup>1</sup>Source: Active Bacterial Core surveillance (ABCs) cases from 2004-2013 estimated to the U.S. population with 18% correction for nonculture confirmed cases. In 2010, estimated case counts from ABCs were lower than cases reported to the National Notifiable Diseases Surveillance System (NNDSS) and might not be representative.
### Menactra® Vaccine Effectiveness Estimates, Duration of Protection, GEE

<table>
<thead>
<tr>
<th>Vaccination Group</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adolescents</td>
<td></td>
</tr>
<tr>
<td>Vaccinated</td>
<td>69% (51%, 80%)</td>
</tr>
<tr>
<td>Serogroup C</td>
<td>77% (57%, 88%)</td>
</tr>
<tr>
<td>Serogroup Y</td>
<td>51% (1%, 76%)</td>
</tr>
<tr>
<td>Vaccinated &lt;1 year</td>
<td>79% (49%, 91%)</td>
</tr>
<tr>
<td>Vaccinated 1-&lt;3 years</td>
<td>69% (44%, 83%)</td>
</tr>
<tr>
<td>Vaccinated 3-&lt;7 years</td>
<td>61% (25%, 79%)</td>
</tr>
</tbody>
</table>

Controls for smoking, underlying condition status, and age
SBA-BR Seroresponse ≥1:128 Post-Vaccination, Menactra®, Serogroup C

*Data courtesy of sanofi pasteur, 3 year follow-up of MTA02 (11-18 year-olds), 5 year follow-up of 603-02 (2-10 year-olds)
What’s going on?

- **Immunologic memory not enough**
  - Boost response takes 5-7 days after exposure, incubation period of *N. meningitidis* is 1-4 days
  - Need circulating antibody at time of exposure

- **Circulating antibody wanes after conjugate vaccine**
  - Approximately 50-60% of persons vaccinated had titers above level required for licensure 5 years after vaccination

- **Unlikely getting the additional benefits of herd immunity with the current U.S. program**
  - Coverage increased slowly
  - Adolescent immunity at population level lower than 60%
SBA-BR Pre- and Post-booster, Menactra®, Serogroup C

*Data courtesy of sanofi pasteur, 5 year follow-up of (11-18 year-olds at dose 1)
Rationale: 2011 Booster Dose Recommendations

- Optimize protection through late adolescence
- Expectation that antibody decline will not be as rapid after the booster dose
- Increase potential for herd immunity
Serogroup B Meningococcal (MenB) Vaccines

- Serogroup B capsular polysaccharide is poorly immunogenic
- Previously developed serogroup B vaccines are clone specific
- Alternative approaches for vaccine development needed

Vaccine 30S:B87,2012
Two MenB Vaccines For Persons Aged 10–25 Years in the United States

- **MenB-FHbp (Trumenba®, Pfizer)**
  - Components: fHbp subfamily A/v2,3; subfamily B/v1
  - 3 dose series, administered at 0, 2, 6 months
  - Licensed in the U.S. on October 29, 2014

- **MenB-4C (Bexsero®, Novartis/GSK)**
  - Components: fHbp subfamily B/v1, NhbA, NadA, Por A1.4
  - 2 dose series, administered at 0 and ≥1 month
  - Licensed in the U.S. on January 23, 2015
  - Licensed in >37 countries for persons ≥2 months of age
Licensure of MenB Vaccines

- Following outbreaks of serogroup B meningococcal disease on two college campuses in 2013 licensure accelerated

- Both MenB vaccines were granted Breakthrough Therapy designations
  - Expedites drug development and review by FDA

- Both MenB vaccines were licensed based on accelerated approval regulations
Options for Use of MenB vaccines

- **Recommendation for groups at increased risk**
  - Medical conditions
    - Persistent complement component deficiencies
    - Anatomic or functional asplenia
  - Microbiologists
  - Outbreak response

- **Routine recommendation for expanded groups**
  - Adolescent or college student recommendation
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

1 Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H, or taking eculizumab (Soliris®)
2 Including sickle cell disease
Challenges when Considering Routine Use of MenB Vaccines in Adolescents

- Proportion of serogroup B cases that could be prevented with MenB vaccines is unknown
  - Breadth of strain coverage estimated; actual breadth of strain coverage unclear
  - Available antibody persistence data suggests limited duration of protection

- Effectiveness data are not available
  - Licensure is based on bactericidal activity
  - Universal programs not implemented in any country to date

- Impact on carriage unknown

- Potential impact of vaccine pressure on circulating strains unknown
## Potential Cases and Deaths Prevented per 4M Cohort

<table>
<thead>
<tr>
<th>Series</th>
<th>Cases Prevented</th>
<th>Deaths Prevented</th>
<th>NNV* to prevent case</th>
<th>NNV to prevent death</th>
<th>Cost ($) per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series at 11 years</td>
<td>15</td>
<td>2</td>
<td>203,000</td>
<td>1,512,000</td>
<td>$8,700,000</td>
</tr>
<tr>
<td>Series at 16 years</td>
<td>28</td>
<td>5</td>
<td>107,000</td>
<td>788,000</td>
<td>$4,100,000</td>
</tr>
<tr>
<td>Series at 18 years</td>
<td>29</td>
<td>5</td>
<td>102,000</td>
<td>638,000</td>
<td>$3,700,000</td>
</tr>
<tr>
<td>College students</td>
<td>9</td>
<td>1</td>
<td>368,000</td>
<td>2,297,000</td>
<td>$9,400,000</td>
</tr>
</tbody>
</table>

*Number needed to vaccinate*

Source: Ismael Ortega-Sanchez
A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. (Category B)
Guidance for Use

- MenB should be administered as either a 2-dose series of MenB-4C or a 3-dose series of MenB-FHbp.
- The same vaccine product should be used for all doses.
- Based on available data and expert opinion, MenB-4C and MenB-FHbp may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible.
- No product preference to be stated.
Summary

- Meningococcal disease is a rare, but serious illness and each case is life-threatening
- Key data on MenB vaccines are not yet available
- Desire for access to MenB vaccines
- Additional work still needed to reinforce the second dose of MenACWY in the current adolescent program
- Risk for disease is low
  - In the absence of vaccination there may be cases that are preventable
  - Even with a fully implemented vaccination program the MenB vaccines will not prevent all cases
Useful References

- “Prevention and Control of Meningococcal Disease” (2013 ACIP Recommendations), MMWR, March 22, 2013
- All ACIP recommendations for meningococcal vaccines: http://www.immunize.org/acip/acipvax_menin.asp
- “Meningococcal Disease” Red Book Chapter
- “Meningococcal Disease” Pink Book Chapter
Questions?
Thank you!

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