Meningococcal Disease and Vaccines

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Neisseria meningitidis

- Gram-negative diplococci
- Humans are the only natural reservoir
- Attach to surface of mucosal cells of nasopharynx
- Approximately 10% of persons are colonized – can carry and transmit bacteria for months
- Transmitted by aerosols or secretions from the nasopharynx of colonized persons
- If infection occurs, it usually occurs within several days of new colonization
Neisseria meningitidis

- Produces a polysaccharide capsule, which is basis of serogroup typing
  - At least 13 serogroups have been identified
- Majority of disease worldwide is serogroup A, B, C, Y, and W
- Serogroups B, C and Y are the most common in the United States
- Serogroup A is common in the “meningitis belt” of sub-Saharan Africa
Meningococcal Disease by Serogroup -- California, 2008-2014*

- **Serogroup B**: 38% (11% fatal, median age 18 years)
- **Serogroup C**: 34% (19% fatal, median age 34.5 years)
- **Serogroup Y**: 19% (10% fatal, median age 48 years)
- **Serogroup W**: 6% (23% fatal, median age 50 years)
- **Ungroupable**: 3%
- Other <1%

Of cases with known serogroup; 30 (4%) unknown
Meningococcal Disease

- Caused by *Neisseria meningitidis*
- Current leading cause of bacterial meningitis:
  - CA: 100-200 cases per year
  - US: 1,200 – 2,800 cases per year
- Incubation period 1-10 days (usually <4 days)
- Even with proper treatment, may progress rapidly and result in death
- Causes substantial morbidity: 10-20% survivors have sequelae (neurologic disability, limb/digit loss, hearing loss, skin scarring)
- Outbreaks account for 2-3% of reported US cases
- Cases typically peak in late winter, early spring
Meningococcal Disease

- Meningococcal disease can present as meningococcal meningitis and/or meningococcemia (bacteremia)
  - *N. meningitidis* is just one cause of bacterial meningitis or sepsis
  - 50% of cases are meningitis; fatality 9-12%
  - 30-40% of cases are meningococcemia; fatality up to 40%
Risk Factors for Meningococcal Disease

• **Host factors**
  - Deficiencies in the terminal common complement pathway
  - Functional or anatomic asplenia
  - Certain genetic factors

• **Environmental factors**
  - Preceding or concurrent viral upper respiratory tract infection
  - Crowded living situations/social situations
  - Active and passive smoking
  - Occupational risk (microbiologists)
Meningococcal Disease Symptoms

Meningitis

- Primary symptoms are sudden onset of fever, headache and stiff neck
  - In infants, fever, headache or stiff neck may be absent or difficult to notice
  - Infants may be inactive, irritable, vomiting or feeding poorly
- Other symptoms
  - Nausea
  - Vomiting
  - Photophobia
  - Altered mental status

Meningococcemia

- Fatigue
- Vomiting
- Cold hands and feet
- Chills
- Severe aches or pain in muscles, joints, chest or abdomen
- Rapid breathing
- Diarrhea
- In the later stages, petechia or purpura may occur
The “Glass Test”

- A fever with a rash that doesn't fade under pressure is a medical emergency.
- If you press the side of a clear glass or glass slide firmly against the skin and the rash doesn't fade, it's a sign of meningococccemia.
- A person with meningococccemia may have a petechial rash that later develops into purpura.
- The rash can be harder to see on dark skin – areas on paler areas like the palms of the hands, soles of the feet, the abdomen, inside the eyelids and on the roof of the mouth can be checked.
The Glass Test

- Press the side of a clear glass or glass slide firmly against the skin to see if it blanches.
- Rash may fade under pressure at first so keep checking at least every hour.
- Even if there is no rash, if someone is ill with the symptoms of meningococcal disease and is getting worse, medical care should be sought immediately.
Laboratory Diagnosis

- Bacterial culture (blood, CSF)
- Gram stain (gram negative diplococci)
  - Note: Gram stains can be misidentified
  - If patient’s symptoms compatible with meningococcal disease treat as such
- Non-culture methods
  - PCR (preferred non-culture method)
    - Can detect *N. meningitidis* DNA in culture negative cases; CDPH lab can perform
    - Important when patient pretreated with antibiotics
  - Antigen detection in CSF
    - False negative results common
  - Serology
    - Should not be used for diagnosis
- Report to public health as soon as meningococcal disease suspected
Medications should include an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone.

Once the microbiologic diagnosis is established, definitive treatment with penicillin G, ampicillin, or an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended.

Some experts recommend susceptibility testing before switching to penicillin, however:

- Susceptibility testing is not standardized, and the significance of intermediate resistance is not known.
- *N. meningitidis* penicillin resistance is rare in the US.
Public Health Actions

- Suspected meningococcal cases should be reported immediately to public health.
- Persons with meningococcal disease are considered infectious <7 days before onset until ≥24 hours after initiation of antibiotic therapy.
- Close contacts are identified and administered chemoprophylaxis (e.g., household members, intimate contacts, some healthcare personnel, first responders):
  - Typically one dose of ciprofloxacin sufficient to clear carriage.
- Bacterial isolates should be submitted to CDPH for serogroup identification and molecular typing.
- Clinical samples (e.g., CSF or blood) should be submitted to CDPH for PCR testing when cultures negative.
Infectious Agent
Neisseria meningitidis, a gram-negative diplococcus bacterium carried by 5-10% of the population.

Clinical Description
Invasive disease manifests most commonly as meningitis and/or meningococcemia and may progress to purpura fulminans, shock, and death within hours of onset. Other manifestations, such as septic arthritis or orbital cellulitis, may be observed. The case fatality rate is 10% and 11-19% of surviving patients have sequelae (e.g., neurologic disability, limb loss, and hearing loss).

Mode of Transmission
Transmission occurs through contact with aerosols from the nose, throat, and mouth of colonized or infected persons. N. meningitidis may be carried in the nasopharynx of otherwise healthy individuals. Invasive meningococcal disease occurs primarily in individuals who are newly colonized with the organism, usually Morbidity and Mortality Weekly Report (MMWR)

Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Recommendations and Reports
March 22, 2013 / 62(RR02):1-22

https://www.cdph.ca.gov/HealthInfo/discond/Pages/MeningococcalDisease.aspx
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm
### 2015 AAP Red Book Recommendations for Postexposure Prophylaxis

#### Table 3.41. Recommended Chemoprophylaxis Regimens for High-Risk Contacts and People With Invasive Meningococcal Disease

<table>
<thead>
<tr>
<th>Age of Infants, Children, and Adults</th>
<th>Dose</th>
<th>Duration</th>
<th>Efficacy, %</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td></td>
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<tr>
<td>&lt;1 mo</td>
<td>5 mg/kg, orally, every 12 h</td>
<td>2 days</td>
<td>90–95</td>
<td>Can interfere with efficacy of oral contraceptives and some seizure and anticoagulant medications; can stain soft contact lenses</td>
</tr>
<tr>
<td>≥1 mo</td>
<td>10 mg/kg (maximum 600 mg), orally, every 12 h</td>
<td>2 days</td>
<td>90–95</td>
<td></td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;15 y</td>
<td>125 mg, intramuscularly</td>
<td>Single dose</td>
<td>90–95</td>
<td>To decrease pain at injection site, dilute with 1% lidocaine</td>
</tr>
<tr>
<td>≥15 y</td>
<td>250 mg, intramuscularly</td>
<td>Single dose</td>
<td>90–95</td>
<td>To decrease pain at injection site, dilute with 1% lidocaine</td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 mo</td>
<td>20 mg/kg (maximum 500 mg), orally</td>
<td>Single dose</td>
<td>90–95</td>
<td>Not recommended routinely, equivalent to rifampin for eradication of <em>Neisseria meningitidis</em> from nasopharynx in one study</td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td></td>
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</tr>
<tr>
<td>10 mg/kg (maximum 500 mg)</td>
<td>Single dose</td>
<td>90–95</td>
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</tr>
</tbody>
</table>

*Not recommended for use in pregnant women.

*Use only if fluoroquinolone-resistant strains of *N meningitidis* have not been identified in the community.
Meningococcal Vaccines

• Polysaccharide vaccine first licensed in 1974
  ▪ Menomune® licensed in 1981 (A, C, W, Y)
  ▪ Only licensed vaccine for adults ≥56 years of age; however, mainly used for meningococcal vaccine naïve persons who anticipate only needing a single dose of vaccine, i.e., travelers

• Conjugate vaccines
  ▪ Menactra® licensed in 2005 (A, C, W, Y)
  ▪ Menveo® licensed in 2010 (A, C, W, Y)
  ▪ MenHibrix® licensed in 2012 (C, Y)

• MenB vaccines
  ▪ Trumenba® licensed in 2014
  ▪ Bexsero® licensed in 2015
Meningococcal Vaccines: Men-ACWY

- Quadrivalent conjugate vaccine, contains capsular polysaccharide antigens to serogroups A, C, Y and W
  - Menactra® licensed 2005 (9 months through 55 years of age)
  - Menveo® licensed in 2010 (2 months through 55 years of age)

- Recommended for all persons aged 11-18 years and high risk persons 2 months-55 years with a booster at age 16 or 5 years after prior dose
  - High risk includes persons with complement component deficiencies or asplenia, laboratory workers, travelers to meningitis belt or Hajj, MSM with multiple sex partners in certain geographic areas
The incidence of meningococcal disease varies over time and by age and location.

During the past 60 years, the annual incidence of meningococcal disease in the US has varied from <0.3 to 1.5 cases per 100,000 population.

Incidence cycles have occurred over multiple years; since the early 2000s, annual incidence rates have decreased.

The reasons for this decrease, which preceded introduction of meningococcal conjugate vaccine into the immunization schedule, are not known but may be related to immunity of the population to circulating meningococcal strains and to the changes in behavioral risk factors (e.g., smoking and exposure to secondhand smoke among adolescents and young adults).
Meningococcal Vaccines: MenB

- Outer polysaccharide capsule mimics the polysaccharide in human neurologic tissue; poorly immunogenic

- Two Men B vaccines are now licensed by FDA (both granted breakthrough therapy status to expedite approval)

- **Trumenba® (Pfizer):** 3 dose series
  - Licensed in October 2014 for use in individuals 10-25 years of age
  - 2 recombinant factor H binding protein (fHBP) variants

- **Bexsero® (GSK):** 2 dose series
  - Licensed in US in January 2015 for use in persons 10-25 years of age
  - Licensed in Europe, Australia and Canada starting at 2 months of age
  - Recommended for routine use in infants in the UK
  - 4 distinct antigens including factor H binding protein (fHbp), Neisserial adhesin A (NadA), Neisserial heparin-binding antigen (NHBA), and PorA antigen of OMV NZ
MenB vaccines in the U.S.

- Advisory Committee of Immunization Practices (ACIP) recommended for high risk persons in Feb 2015
  - Persons with persistent complement component deficiencies
  - Persons with anatomic or functional asplenia
  - Microbiologists routinely exposed to isolates of *N. meningitidis*
  - Persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak

- ACIP will discuss and vote on MenB vaccine use in healthy adolescents on June 24th

- MenB vaccine can be administered to non-high risk patients at this time but it may not be covered by insurance until there is an category A or B ACIP recommendation
## Current ACIP Recommendations for Meningococcal Vaccines

All ACIP recommendations available at: [http://www.cdc.gov/vaccines/hcp/acip-recs/](http://www.cdc.gov/vaccines/hcp/acip-recs/)

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### Table 3.42. Recommended Meningococcal Vaccines for Immunocompetent Children and Adults

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mo through</td>
<td>MenACWY-D* (Menactra, Sanofi Pasteur, Swiftwater, PA)</td>
<td>Not routinely recommended; see Table 3.43 (p. 555) for recommendations for people at increased risk</td>
</tr>
<tr>
<td>10 y</td>
<td>MenACWY-CRM* (Menveo, Novartis, Cambridge, MA)</td>
<td></td>
</tr>
<tr>
<td>10 through</td>
<td>HibMenACWY-IT* (MenHib, GlaxoSmithKline, Research Triangle Park, NC)</td>
<td></td>
</tr>
<tr>
<td>25 y</td>
<td>rLP2086 serogroup B (Trumembas, Pfizer Inc, Philadelphia, PA) or 4CmEN serogroup B (Bezzerbo, Novartis Vaccines and Diagnostics, Siena, Italy)</td>
<td>Not routinely recommended; see text of 4th bullet (below) for recommendations for people at increased risk</td>
</tr>
<tr>
<td>11 through</td>
<td>MenACWY-D or MenACWY-CRM</td>
<td>Primary:</td>
</tr>
<tr>
<td>21 y</td>
<td></td>
<td>• 11 through 12 y of age, 1 dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 13 through 18 y of age, 1 dose if not previously immunized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 19 through 21 y of age, not routinely recommended but may be given as catch-up immunization for those who have not received a dose after their 16th birthday</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Booster:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 dose recommended for adolescents if first dose administered prior to 16th birthday</td>
</tr>
<tr>
<td>22 through</td>
<td>MenACWY-D or MenACWY-CRM</td>
<td>Not recommended routinely; see Table 3.43 (p. 555) for people at increased risk</td>
</tr>
<tr>
<td>55 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥56 y</td>
<td>MPSV4, MenACWY-D, or MenACWY-CRM</td>
<td>Not routinely; see Table 3.43 for people at increased risk</td>
</tr>
</tbody>
</table>

*Licensed only for people 6 months through 55 years.  
*Licensed only for people 5 months through 55 years.  
*Licensed only for children aged 6 weeks through 10 months of age.
Meningococcal Disease and College Students

- College aged persons, particularly first year students in residence halls, are at increased risk of meningococcal disease
- Many colleges and universities require meningococcal conjugate vaccine and other vaccines, but there has not been such a requirement for the UC/CSU systems
  - However, the UC system recently announced that students entering in fall 2017 will be required to show proof of immunization, including meningococcal conjugate vaccine
  - There is an existing rule in California that institutions with on-campus housing must inform students about meningococcal disease and vaccine (Health and Safety Code, Sections 120395-120399)
Meningococcal Disease and College Students

- Prior to the introduction of conjugate vaccines, serogroup C caused most outbreaks - because most college students are immunized against serogroup C disease, serogroup B outbreaks now occur.

- Since 2009, 41 cases have been identified in California college students – the 36 with known serogroups are shown.

- Most cases are not associated with other cases, however even one case can trigger public anxiety.
Recent US College Outbreaks

- Ohio University: 2008 – 2010
  - 10 cases serogroup B; 3 unknown serogroup
  - MenB vaccine not yet available

- Princeton University: March 2013 – late 2014
  - 8 cases serogroup B in Princeton students
  - 1 outbreak-associated case in a Drexel student
  - Bexsero administered

- UC Santa Barbara
  - 5 cases serogroup B
  - Bexsero administered

- University of Oregon: late Jan 2015 – present
  - 7 cases serogroup B
  - Trumenba administered

- Providence College: Feb 2015
  - 2 cases serogroup B
  - Trumenba administered

- 200-1400 fold increased risk during outbreaks
# Meningococcal Vaccine Recommendations* for Civilian Populations Around the World

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andorra</td>
<td>C at 2m, 4m, 18m</td>
</tr>
<tr>
<td>Australia</td>
<td>C at 12m</td>
</tr>
<tr>
<td>Austria</td>
<td>C at 12-14m, ACWY at 12y</td>
</tr>
<tr>
<td>Bahrain</td>
<td>ACWY at 2y for risk groups</td>
</tr>
<tr>
<td>Belgium</td>
<td>C at 15m</td>
</tr>
<tr>
<td>Brazil</td>
<td>C at 3m, 5m, 15m and AC at &gt;2y for risk groups</td>
</tr>
<tr>
<td>Canada</td>
<td>varies by province; all 13 provinces have 1-3 infant C doses (9 have 1 dose at 12m) and 11 provinces have additional C doses at 9-15y</td>
</tr>
<tr>
<td>Chile</td>
<td>ACWY at 12m</td>
</tr>
<tr>
<td>China</td>
<td>AC at 3y, 6y and A at 6-18m + 3m</td>
</tr>
<tr>
<td>Cuba</td>
<td>BC at 3m, 5m</td>
</tr>
<tr>
<td>Cyprus</td>
<td>C at 12-15m, ACWY (MPSV) at &gt;2y for risk groups</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>B at 2-11 months, B and ACWY at 12m-5y, 12-19 years</td>
</tr>
<tr>
<td>Ecuador</td>
<td>B and C for risk groups</td>
</tr>
<tr>
<td>Egypt</td>
<td>AC at 3m, 6m, 12m, 15y</td>
</tr>
<tr>
<td>France</td>
<td>C at 12-23m, catch-up 2-24y</td>
</tr>
<tr>
<td>Germany</td>
<td>C at 11-23m, catch-up 2-17y</td>
</tr>
<tr>
<td>Greece</td>
<td>C at 2m, 4m, 6m-6y, ACWY at 11y</td>
</tr>
<tr>
<td>Guyana</td>
<td>ACW for risk groups</td>
</tr>
<tr>
<td>Iceland</td>
<td>C at 6m, 8m and ACWY for travelers</td>
</tr>
<tr>
<td>Ireland</td>
<td>C at 4m, 6m, 13m</td>
</tr>
<tr>
<td>Israel</td>
<td>ACWY for risk groups</td>
</tr>
<tr>
<td>Italy</td>
<td>C at 13-15m, catch-up 11-18y</td>
</tr>
<tr>
<td>Jordan</td>
<td>ACWY at &gt;2y for contacts, pilgrims</td>
</tr>
<tr>
<td>Kuwait</td>
<td>ACWY at 2y, AC for expatriot risk groups</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>ACWY at 15y for travelers</td>
</tr>
<tr>
<td>Libya</td>
<td>ACWY at 6y for pilgrims</td>
</tr>
<tr>
<td>Liechtenstein</td>
<td>C at 12-15m, catch-up 11-15y</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>C at 13m</td>
</tr>
<tr>
<td>Malaysia</td>
<td>ACWY for pilgrims</td>
</tr>
<tr>
<td>Maldives</td>
<td>ACWY at &gt;15y for pilgrims</td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>C at 11-12y</td>
</tr>
<tr>
<td>Mauritius</td>
<td>ACWY for travelers</td>
</tr>
<tr>
<td>Monaco</td>
<td>C at 12m</td>
</tr>
<tr>
<td>Netherlands</td>
<td>C at 14m</td>
</tr>
<tr>
<td>New Zealand</td>
<td>C at &lt;2y and ACWY at &gt;2y for risk groups, contacts of cases, those living in close quarters</td>
</tr>
<tr>
<td>Oman</td>
<td>ACWY at 2y</td>
</tr>
<tr>
<td>Palau</td>
<td>C at 11-18y</td>
</tr>
<tr>
<td>Paraguay</td>
<td>AC for risk groups</td>
</tr>
<tr>
<td>Poland</td>
<td>C at 2-6m, 8m-19y</td>
</tr>
<tr>
<td>Portugal</td>
<td>C at 12m</td>
</tr>
<tr>
<td>Qatar</td>
<td>ACWY for risk groups</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>ACWY at &gt;2y</td>
</tr>
<tr>
<td>Serbia</td>
<td>AC for risk groups</td>
</tr>
<tr>
<td>Slovenia</td>
<td>C and ACWY for risk groups</td>
</tr>
<tr>
<td>Spain</td>
<td>C at 2m, 12m, 12y</td>
</tr>
<tr>
<td>Switzerland</td>
<td>C at 12-15m, 11-15y</td>
</tr>
<tr>
<td>Suriname</td>
<td>ACWY for travelers</td>
</tr>
<tr>
<td>Syria</td>
<td>ACWY at 6y</td>
</tr>
<tr>
<td>Togo</td>
<td>A at 1-29y</td>
</tr>
<tr>
<td>Trinidad/Tobago</td>
<td>AC at &gt;2y mainly for travelers</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>risk groups, pilgrims</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>B at 2m, 4m, 12m, C at 3m, 12-13m, ACWY at 14-15y</td>
</tr>
<tr>
<td>Venezuela</td>
<td>B and C at days 1 and 2 of life for risk groups</td>
</tr>
</tbody>
</table>

*Routine vaccination unless otherwise specified; as of 4/6/2015