Conflict of Interest Declaration

• Drs. Miller and Nikocevic declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Pharmacist Objectives

• Describe the etiology and epidemiology of HZ
• Describe the clinical presentation of HZ
• Compare and contrast zoster vaccines (Zostavax® and Shingrix®)
• Describe the etiology and epidemiology of meningococcal disease
• Discuss risk factors for meningococcal disease
• Describe the clinical presentation of meningococcal disease
• Compare and contrast meningococcal B vaccines (Trumenba® and Bexsero®)
Pharmacy Technician Objectives

- Describe the etiology and epidemiology of HZ
- Describe the clinical presentation of herpes zoster
- Describe the etiology and epidemiology of meningococcal disease
- Discuss risk factors for meningococcal disease
- Describe the clinical presentation of meningococcal disease
1. Which of the following is TRUE regarding herpes zoster (HZ)?

a. HZ usually presents as a localized, unilateral, painful rash
b. Herpes zoster is the infection that occurs after the initial exposure to VZV
c. HZ is more common in adults younger than 50 years of age
d. The symptoms of herpes zoster prodrome include severe GI upset
2. Which of the following is TRUE regarding live zoster vaccine (Zostavax®)?
   a. Zostavax® is contraindicated in patients taking prednisone 50 mg PO once daily longterm
   b. Zostavax® should never be administered within 4 weeks of Pneumovax-23®
   c. Zostavax® is administered in the dose of 0.65 ml IM as a single dose
   d. Zostavax® can be administered to a patient who had cancer and has been in remission for 9 months
Pre-Test Questions

3. Which of the following is a side effect commonly associated with recombinant, adjuvanted zoster vaccine (Shingrix®)?

a. Paresthesias
b. Blurred vision
c. Tachycardia
d. Diarrhea
4. Which of the following serogroups is the most common cause of meningococcal disease in patients 16-24 years of age?
   a. A
   b. B
   c. C
   d. W
   e. Y
HERPES ZOSTER
Herpes Zoster

- Localized, generally painful rash\(^1\)
- 1 in 3 persons will develop zoster during their lifetime

\(^1\)CDC. Prevention of herpes zoster. MMWR 2008;57(RR-5):1-30.
Etiology

• Caused by varicella zoster virus (VZV) reactivation from dorsal root and cranial nerve ganglia\(^2\)
• VZV spreads from a single ganglion to the neural tissue of the affected segment and the corresponding cutaneous dermatome

Epidemiology

• Estimated 1 million episodes in US annually\(^1\)
• Risk factors
  • Age\(^3\)
  • Altered cell mediated immunity
  • Neoplastic diseases
  • Immunosuppressive therapy
  • Organ transplant recipients
  • HIV positive
  • Gender\(^4\)
  • Race\(^5\)
  • Inflammatory diseases\(^1\)

\(^1\)CDC. Prevention of herpes zoster. MMWR 2008;57(RR-5):1-30.
Clinical Presentation

• Prodrome\(^3\)
  • Headache
  • Photophobia
  • Malaise
  • Fever
  • Pain
    • Aching, stabbing, burning, shock-like
  • Abnormal skin sensations

Clinical Presentation

• Brief erythematous, macular rash, followed by rapid development of papules
• Papules develop into vesicles within 1-2 days
• Vesicles continue to appear for 3-4 days
• Pustulation begins within 1 week, followed 3-5 days later by ulceration and crusting
• Crusts disappear in 3-4 weeks

Clinical Presentation

- Rash is unilateral\(^2\)
- Single dermatome is affected
- Accompanied by pain

Treatment of HZ

- Antiviral therapy\(^2\)
- Oral corticosteroids
- Analgesic treatments
- Neural blockade
- Other treatments
  - VZV hyperimmune globulin
  - Percutaneous electrical nerve stimulation
  - Topical capsaicin

Prevention of Herpes Zoster

- Live zoster vaccine (Zostavax®)
- Recombinant, adjuvanted zoster vaccine (Shingrix®)
Live zoster vaccine (Zostavax®)

- Live, attenuated vaccine indicated for prevention of herpes zoster in individuals 50 years of age and older\textsuperscript{10}
- 19,400 plaque-forming units per 0.65 ml dose when reconstituted
- Dose
  - 0.65 ml administered via subcutaneous injection as a single dose

Contraindications/Precautions

- History of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other vaccine component\textsuperscript{10}
- Immunosuppression or immunodeficiency
- Pregnancy
- Defer in acute illness or with active, untreated tuberculosis
- Consider administering 4 weeks apart from Pneumovax-23\textsuperscript{®}

Adverse Reactions

- Headache\textsuperscript{10}
- Injection site reactions
  - Pain
  - Swelling
  - Redness
  - Itching

Live Zoster Vaccine Landmark Studies

- Shingles Prevention Study (SPS)
- Short-Term Persistence Substudy (STPS)
- Long-Term Persistence Substudy (LTPS)
- Zostavax Efficacy, Safety and Tolerability Study (ZEST)
Shingles Prevention Study (SPS)

- Randomized, placebo controlled, double blind clinical trial at 22 sites\(^4\)
- 38,546 subjects enrolled from 11/1998 to 09/2001
- Inclusion criteria
  - \(\geq 60\) years of age
  - History of varicella or resided in continental US for at least 30 years
- Exclusion criteria
  - Immunocompromised patients
  - Those unable to adhere to protocol

Shingles Prevention Study (SPS)

• Intervention\(^4\)
  • 0.5 ml of live attenuated Oka/Merck zoster vaccine (median potency 24,600 PFU) or placebo

• Endpoints
  • Burden of Illness
    • Measure of total pain and discomfort associated with HZ in study population
  • Incidence of PHN
    • Pain associated with HZ that was rated as 3 or more on a scale from 0-10, persisting or appearing more than 90 days after the onset of rash

SPS-Results

- $\text{VE}_{\text{BOI}}$ was 61.1% (95% CI 51.1-69.1)$^4$
- $\text{VE}_{\text{PHN}}$ was 66.5% (95% CI 47.5-79.2)
- $\text{VE}_{\text{HZ}}$ was 51.3% (95% CI 44.2-57.6)

SPS-Vaccine Safety

• Injection site reactions in vaccine group
  • Erythema in 35.8 % of subjects
  • Pain or tenderness in 34.5 % of subjects
  • Swelling in 26.2 % of subjects
  • Pruritus in 7.1 % of subjects

• Serious adverse events
  • 1.9 % in vaccine group vs. 1.3% in placebo group, P=0.03

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Short-Term Persistence Substudy (STPS)

- Re-enrolled 7320 vaccine and 6950 placebo recipients from SPS\textsuperscript{11}
- Extended the follow up of this cohort to collect data on persistence of zoster vaccine efficacy for BOI, PHN, and HZ
- Inclusion/exclusion criteria
  - Same as SPS
  - Patients who received shingles vaccine were not excluded
- Follow up started in December 2004, and ended in March 2006
- Endpoints
  - $\text{VE}_{\text{BOI}}, \text{VE}_{\text{PHN}}, \text{VE}_{\text{HZ}}$ for STPS population, SPS+STPS population, and for each year through year 7 after vaccination

STPS-Results

• STPS Population\textsuperscript{11}
  • \(V_{E_{BOI}}\) was 50.1\% (95\% CI 14.1-71.0)
  • \(V_{E_{PHN}}\) was 60.1\% (95\% CI -9.8-86.7)
  • \(V_{E_{HZ}}\) was 39.6\% (95\% CI 18.2-55.5)

• STPS and SPS Population
  • \(V_{E_{BOI}}\) was 58.6\% (95\% CI 48.6-66.6)
  • \(V_{E_{PHN}}\) was 64.9\% (95\% CI 47.4-77.0)
  • \(V_{E_{HZ}}\) was 48.7\% (95\% CI 42.0-54.7)

STPS-Results\textsuperscript{11}

Long-Term Persistence Substudy (LTPS)

- Re-enrolled 6867 participants from SPS and STPS (6546 from STPS) between March 2006 and June 2007\textsuperscript{12}
- Surveillance for HZ ended on 12/30/2010
- Inclusion/exclusion criteria
  - Same as SPS and STPS
- Endpoints
  - $\text{VE}_{\text{BOI}}$, $\text{VE}_{\text{PHN}}$, $\text{VE}_{\text{HZ}}$ for up to 11 years post-vaccination for SPS vaccine recipients

LTPS-Results$^{12}$

LTPS-Results\textsuperscript{12}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Graph showing vaccine efficacy over time.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Years After Vaccination & Primary & Sensitivity I & Sensitivity II & SPS & STPS \\
\hline
1 & 47.7 & 41.2 & 50.9 & 79.2 & 74.9 \\
2 & 46.2 & 39.5 & 49.1 & 54.9 & 23.6 \\
3 & 27.6 & 18.6 & 31.1 & 44.4 & \\
4 & 33.3 & 25.1 & 36.0 & 66.9 & \\
5* & 7.9 & -3.3 & 11.1 & & \\
6* & & & & & \\
7* & & & & & \\
8* & & & & & \\
9 & & & & & \\
10 & & & & & \\
11 & & & & & \\
\hline
\end{tabular}
\end{table}

LTPS-Results\textsuperscript{12}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ltps_results}
\end{figure}

\begin{tabular}{lcccc}
& Primary & & & \\
Years After Vaccination & 1 & 2 & 3 & 4 & 5\textsuperscript{*} & 6\textsuperscript{*} & 7\# & 8\# & 9 & 10 & 11 \\
Sensitivity II & 26.3 & 27.5 & 60.5 & 44.2 & 11.5 \\
SPS & 83.4 & 69.8 & 38.3 & 60.7 \\
STPS & 24.6 & 25.3 & 58.9 & 41.4 & 6.2 \\
\end{tabular}

\begin{tabular}{lcccc}
& & & & \\
Primary & & & & \\
Sensitivity II & 73.8 & 32.0 \\
SPS & & & & \\
STPS & & & & \\
\end{tabular}

\textsuperscript{12}\textit{Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. CID 2015;60:900-9.}
ZEST

• Randomized, placebo controlled, double blind multicenter study\textsuperscript{13}
• Conducted in North America and Europe between 10/2007 and 01/2010
• 22,439 participants randomized to zoster vaccine or placebo

• Inclusion criteria
  • Healthy subjects aged 50-59 years
  • History of varicella or residence in VZV endemic area for \geq 30 years

• Exclusion criteria
  • Immune compromise due to disease (cancer, HIV) or treatments (corticosteroids, chemotherapy, transplant recipients)

**ZEST**

- **Intervention**\(^\text{13}\)
  - 0.65 ml subcutaneous injection of zoster vaccine or placebo in the deltoid area

- **Endpoints**
  - # of cases of HZ
  - Determination of confirmed HZ cases
  - Safety

ZEST-Results\textsuperscript{13}

- 129 confirmed cases of HZ
  - 30 in ZV group, 99 in placebo group
- PCR positive in 111 of the 129 cases
  - 24 in ZV group, 87 in placebo group
- $VE_{HZ}$ was 69.8\% (95\% CI 54.1-80.6)
- Relative reduction in severity-by-duration pain score was 73\% (95\% CI 52.7-84.6)

ZEST-Results

- Adverse events
  - 72.8% of subjects in vaccine group vs. 41.5% of subjects in placebo group
    - Higher rates of injection site reactions and headache in vaccination group
  - No significant differences in the proportion of subjects reporting adverse events within 42 and 182 days post-vaccination

Two Dose Schedule Studies

Recombinant, adjuvanted zoster vaccine (Shingrix®)

- Recombinant, adjuvanted zoster vaccine indicated for prevention of herpes zoster in individuals 50 years of age and older\textsuperscript{10}
- Lyophilized VZV glycoprotein E antigen component reconstituted with AS01\textsubscript{B} adjuvant suspension
- Dose
  - 0.5 ml administered via intramuscular injection at 0 and 2-6 months

Contraindications/Precautions

• History of anaphylactic/anaphylactoid reaction to any other vaccine component\textsuperscript{10}
• Immunosuppression or immunodeficiency?
• Pregnancy

Adverse Reactions

- Pain, redness, swelling
- Fatigue
- Headache
- Shivering
- Fever
- GI
  - N/V/D, abdominal pain

Zoster Recombinant, Adjuvanted Vaccine Landmark Studies

- ZOE-50
- ZOE-70
- Zoster 048
ZOE-50

• Ongoing, randomized, placebo controlled study conducted in 18 countries\textsuperscript{14}
• 16,160 participants were enrolled between 08/02/2010 and 07/21/2011
• Inclusion criteria
  • 50 years of age or older
• Exclusion criteria
  • History of HZ
  • Previously vaccinated against varicella or HZ
  • Immunosuppressive condition

ZOE-50-Intervention

• 0.5 ml IM (deltoid) HZ/su vaccine or placebo at months 0 and 2\textsuperscript{14}
  • HZ/su vaccine contains 50 mcg of recombinant VZV glycoprotein E and the liposome-based AS0\textsubscript{1B} adjuvant system containing 50 mcg of 3-\textit{O}-desacyl-4’-monophosphoryl lipid A (MPL) and 50 mcg of \textit{Quillaja saponaria} Molina, fraction 21 (QS21, Antigenics, a wholly owned subsidiary of Agenus)
  • Placebo: 0.9 % NaCl

ZOE-50-Endpoints

- Efficacy\textsuperscript{14}
  - Number of cases of HZ
- Reactogenicity
  - Solicited injection site and systemic reactions for 7 days after vaccination
  - Scale from 0-3 (0=absent, 3=prevents ADLs)

ZOE-50-Efficacy Results

- 408 reported cases of suspected HZ\textsuperscript{14}
- 244 confirmed cases of HZ
- 216 confirmed cases of HZ in modified vaccinated cohort
  - 6 in HZ/su group and 210 in placebo group
  - HZ incidence per 1000 person-years:
    - 0.3 in the HZ/su group and 9.1 in the placebo group
- Overall vaccine efficacy 97.2 \% (CI 93.7-99.0, p<0.001)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>HZ/su group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sxs within 7 days after vaccination</td>
<td>84.4 %</td>
<td>37.8 %</td>
</tr>
<tr>
<td>Grade 3 symptoms</td>
<td>17 %</td>
<td>3.2 %</td>
</tr>
<tr>
<td>Pain</td>
<td>79.1 %</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Myalgia</td>
<td>46.3 %</td>
<td>12.1 %</td>
</tr>
<tr>
<td>Serious ADR’s within 30 days</td>
<td>103 (87 of 7698 subjects)</td>
<td>128 (97 of 7713 subjects)</td>
</tr>
</tbody>
</table>

ZOE-70

- Performed concurrently with ZOE-50\textsuperscript{15}
- Same study design as ZOE-50
- Inclusion criteria
  - 70 years of age or older
- Exclusion criteria
  - History of HZ
  - Previously vaccinated against varicella or HZ
  - Immunosuppressive conditions

ZOE-70 Endpoints

• **Efficacy**
  • Reducing risk of HZ and PHN in patients 70 years of age or older

• **Pooled analysis of ZOE-50 and ZOE-70**
  • Efficacy in reducing risk of PHN among participants age 70 and older from the two studies
  • Efficacy against PHN among participants 50 years of age or older and the evaluation of vaccine safety and reactogenicity

ZOE-70-Efficacy Results

- 432 reported cases of suspected HZ\textsuperscript{15}
- 270 confirmed cases of HZ
- 246 confirmed cases of HZ in modified vaccinated cohort
  - 23 in HZ/su group and 223 in placebo group
    - Mean follow up period 3.7 years
  - HZ incidence per 1000 person-years:
    - 0.9 in the HZ/su group and 9.2 in the placebo group
- Overall vaccine efficacy 89.8 % (CI 84.2-93.7, p<0.001)

ZOE-70-Pooled Analysis Efficacy Results

- 309 confirmed cases of HZ\textsuperscript{15}
  - 25 in HZ/su group and 284 in placebo group
- Vaccine efficacy 91.3 % (CI 86.8-94.5, p<0.001)
- Vaccine efficacy
  - 97.6 % during year 1
  - 92.0 % during year 2
  - 84.7 % during year 3
  - 87.9 % during year 4

ZOE-70-PHN Efficacy Results

- Pooled modified vaccination cohort of all participants 50 years of age or older\textsuperscript{15}
  - 4 of 32 in HZ/su group and 46 of 477 in placebo group
- Incidence of PHN per 1000 person years
  - 0.1 in HZ/su group and 0.9 in placebo group
- $V_{E_{PHN}}$ 91.2\% among adults 50 years of age and older (CI 75.9-97.7, $P<0.001$)
- No PHN in participants younger than 70
- $V_{E_{PHN}}$ in adults 70 years of age and older was 88.8\% (CI 68.7-97.1, $p<0.001$)

ZOE-70-Reactogenicity Results\textsuperscript{16}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>HZ/su group (%)</th>
<th>Placebo group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sxs within 7 days after vaccine</td>
<td>79.0</td>
<td>29.5</td>
</tr>
<tr>
<td>Grade 3 sxs</td>
<td>8.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>74.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Pain</td>
<td>68.7</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.9</td>
<td></td>
</tr>
</tbody>
</table>

Zoster 048

- Phase 3, open label, group matched, multicenter study conducted in US
- Inclusion criteria
  - Adults ≥ 65 years old vaccinated with live ZV ≥ 5 years ago
  - Group matched to live ZV naive adults
- Exclusion criteria
  - Received or scheduled to receive a live vaccine, investigational or unregistered drug or vaccine w/in 30 days
  - Received immunosuppressants for ≥ 14 days in w/in 180 days
  - Received long acting-immune modifying drugs w/in 180 days before the first HZ/su vaccination
  - History of HZ
  - History of reaction or hypersensitivity to any accine components

Zoster 048-Intervention

- 2 IM doses (deltoid) of HZ/su 2 months apart
  - 50 mcg of gE antigen and AS01$_B$ Adjuvant System

Zoster 048-Endpoints

• Co-primary
  • Humoral immune responses 1 month after dose 2 of HZ/su between the groups
  • Safety and reactogenicity up to 1 month after dose 2

• Secondary
  • Humoral and CMI responses to HZ/su at baseline, and 1 month post dose 1 and post dose 2

Zoster 048-Results

# Zoster 048-Safety Results

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HZ-NonVac (n = 214)</th>
<th></th>
<th>HZ-PreVac (n = 215)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. a</td>
<td>% (95% CI)</td>
<td>No. a</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Solicited AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within the 7-day (days 0–6) postvaccination period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants reporting any solicited local reaction</td>
<td>187</td>
<td>87.4 (82.2–91.5)</td>
<td>193</td>
<td>89.8 (84.9–93.5)</td>
</tr>
<tr>
<td>Grade 3 solicited local reactions</td>
<td>21</td>
<td>9.8 (6.2–14.6)</td>
<td>21</td>
<td>9.8 (6.1–14.5)</td>
</tr>
<tr>
<td>Participants reporting any solicited systemic reaction</td>
<td>154</td>
<td>72.0 (65.4–77.9)</td>
<td>149</td>
<td>69.3 (62.7–75.4)</td>
</tr>
<tr>
<td>Grade 3 solicited systemic reactions</td>
<td>24</td>
<td>11.2 (7.3–16.2)</td>
<td>23</td>
<td>10.7 (6.9–15.6)</td>
</tr>
<tr>
<td></td>
<td>HZ-NonVac (n = 215a)</td>
<td></td>
<td>HZ-PreVac (n = 215a)</td>
<td></td>
</tr>
<tr>
<td><strong>Unsolicited AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within the 30-day (days 0–29) postvaccination period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total reported unsolicited AEs</td>
<td>83</td>
<td>—</td>
<td>125</td>
<td>—</td>
</tr>
<tr>
<td>Participants reporting any unsolicited AE</td>
<td>52</td>
<td>24.2 (18.6–30.5)</td>
<td>78</td>
<td>36.3 (29.8–43.1)</td>
</tr>
<tr>
<td>Unsolicited AEs considered related by investigator</td>
<td>12</td>
<td>5.6 (2.9–9.5)</td>
<td>13</td>
<td>6.0 (3.3–10.1)</td>
</tr>
<tr>
<td>Grade 3 unsolicited AEs</td>
<td>5</td>
<td>2.3 (1.8–5.3)</td>
<td>14</td>
<td>6.5 (3.6–10.7)</td>
</tr>
<tr>
<td><strong>SAEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From the first vaccination up to 30 days after last vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total reported SAEs</td>
<td>4</td>
<td>—</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Participants reporting any SAE</td>
<td>4</td>
<td>1.9 (1.5–4.7)</td>
<td>4</td>
<td>1.9 (1.5–4.7)</td>
</tr>
<tr>
<td>SAEs considered related by investigator</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>pIMDs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From the first vaccination up to 30 days after last vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total reported pIMDs</td>
<td>0</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Zoster 048-Solicited ADRs

MENINGOCOCCAL DISEASE
Meningococcal Disease

• Caused by *Neisseria meningitidis*\(^1\)

• Commonly presents as meningitis, bacteremia or bacteremic pneumonia

• Symptoms occur rapidly, can be fatal within 24 hours

Clinical Presentation

- Sudden fever
- Muscle aches
- Chills
- Headaches
- Vomiting
- Sensitivity to light
- Confusion
- Neck stiffness
- Petechial or purpuric rash
- Hypotension

Petechial or Purpuric Rash


http://healthfixit.com/petechiae-petechia-pictures-causes-diagnosis-treatment
Transmission

- Transmitted through respiratory secretions\(^1\)
  - Kissing
  - Utensils
  - Drinking containers
  - Vaporizers
  - E-cigarettes

Morbidity and Mortality

• Case to fatality rate is 10-15%³
• 20% of survivors experience permanent sequelae
  • Neurologic disability
  • Limb or digit loss
  • Hearing loss

Risk Factors

- **Age**
  - Infants under 1 year old
  - Teens and young adults 16-23 years old
- **Community Setting**
  - Living in close quarters
  - College campuses
  - Schools
  - Military Barracks
- **Medical Conditions**
  - HIV
  - Asplenia and sickle cell
  - Late complement pathway deficiencies
- **Travel**
  - Travel to the sub-Saharan Africa, the meningitis belt

---

Meningococcal Disease Incidence

Meningococcal Disease Incidence by Age 2006-2015

Meningococcal Disease

• Only infects humans\(^3\)
• Colonizes the nasopharynx\(^3,4\)
• Carriage rates highest in adolescents and adults\(^4\)

N. Meningitidis

• Inner and outer membrane separated by a cell wall

• Protein structures on outer membrane enable it to interact with the host cells.

• Encapsulated by a polysaccharide


Meningococcal Serogroups

• Classified into 13 serogroups based on the characteristics of the polysaccharide capsule\(^2\)

• A, B, C, W and Y serogroups are responsible for most meningococcal disease in the world

• Serogroup B causes about 50% of all meningococcal disease in patients 16-24 years of age\(^5\)

---


Conjugate Vaccines

• Capsular polysaccharide based\(^6\)
• Current options available in the United States:
  • Menveo\(^\circledR\) (GSK)
    • Licensed in 2010
    • Quadrivalent (coverage for A, C, Y and W)
  • Menactra\(^\circledR\) (Sanofi)
    • Licensed in 2005
    • Quadrivalent (coverage for A, C, Y and W)
  • Current ACIP recommendations: 1\(^{st}\) dose at 11-12 years old with a booster dose at age 16

Challenges with Development of MenB Vaccines

• MenB polysaccharide resembles neural cell adhesion molecules\(^7\)
  • Poorly immunogenic
• Reverse vaccinology used
  • Sequenced the bacterial genome to find proteins unique to the bacterial wall that could be used as antigens to stimulate immunity
• Led to the discovery of Factor H binding protein\(^8\)


Factor H binding protein (fHbp)

- Outer membrane lipoprotein present on nearly all strains\(^9\)
- Virulence factor for \textit{n. meningitidis} and target for bactericidal antibodies\(^1\)
- Critical for the survival in the human host\(^1\)
- 2 subfamilies: A and B

Serogroup B Outbreaks

• Most cases of meningococcal disease are sporadic (98%) outbreaks account for (2%)\textsuperscript{10}

• 7 Outbreaks that resulted in 41 cases, 3 deaths have been reported at universities or colleges since 2009-2013\textsuperscript{11}

• Most recent outbreaks at Princeton and Santa Clara led to the accelerated approval of the 2 MenB vaccines


Early FDA approval of MenB Vaccines

- MenB-FHbp (Trumenba®), Pfizer\textsuperscript{11}
  - Licensed in 2014
  - For persons 10-25 years old
- MenB-4C (Bexsero®), GSK
  - Licensed in 2015
  - For persons 10-25 years old

MenB-FHbp, Trumenba®

• 2 components\textsuperscript{12}
  • 2 FHbp protein subfamilies A and B

• Also known as bivalent rLP2086

\textsuperscript{12}Folaranmi T, Rubin L, Martin SW, et al; for Centers for disease control and prevention. Use of serogroup B meningococcal vaccines in persons aged ≥ 10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR. 2015; 64:608-612.
MenB-4C (Bexsero®)

- 4 components\(^{13}\)
  - Factor H binding protein (FHbp)
  - Neisserial adhesin A (NadA)
  - Neisserial heparin-binding antigen (NHba)
  - Outer-membrane vesicles (PorA)

\(^{13}\)Serruto D, Bottomley MJ, Ram S. The new multicomponent vaccine against meningococcal serogroup 4CMenB: immunological, functional and structural characterization of the antigens. Vaccine. 2011-2012;30 (S2):B87-97.
Clinical Trial Endpoints

- Vaccine efficacy-determined from serum bactericidal antibodies against selected serogroup strains\textsuperscript{11}
  - hSBA-serum bactericidal assay with human complement
- Immunogenicity-measured by:
  - the proportion of participants that achieved hSBA titer of 4 or more against the tested strain
  - The proportion of participants that achieved a titer the lower limit of quantitation (LLOQ) for all strains, a composite response

MenB-FHpb Immunogenicity Summary

- Immunogenicity and safety was evaluated in 7 clinical trials, 5 randomized controlled trials and 2 open-label studies\(^{11}\)
- 84% of adolescents had a composite hSBA response to 4 strains after 3 doses
- 50% had a composite hSBA response after 2 doses
- 3 of the 7 trials evaluated concomitant administration with other vaccines
- Antibody response was not affected except for HPV type 18

# Clinical Trials Summary of MenB-FHbp Immunogenicity 1 Month Post Dose 3

<table>
<thead>
<tr>
<th>Study description</th>
<th>n</th>
<th>Age</th>
<th>4-fold hSBA response %</th>
<th>Composite hSBA response %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Placebo Controlled Trial Australia, Poland and Spain 3 Strains(^\text{14})</td>
<td>539</td>
<td>11-18</td>
<td>71-94</td>
<td>80-82</td>
</tr>
<tr>
<td>Randomized Controlled United States(^\text{15})</td>
<td>2648</td>
<td>10-13</td>
<td>84-85.7</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Multicenter Randomized United States(^\text{16})</td>
<td>813</td>
<td>11-17</td>
<td>Not assessed</td>
<td>81-84</td>
</tr>
</tbody>
</table>


MenB-FHpb Immunogenicity Extension Summary

- Randomized, single-blind, placebo-controlled extension\textsuperscript{11}
- Blood samples for immunogenicity at 4 intervals
- After 6 months, hSBA responses initially decreased and remained stable thereafter
- After 48 months, 50% of those vaccinated continued to demonstrate protective hSBA titers to 3 of the 4 strains tested

Conclusions

- MenB vaccines provide short-term protection\textsuperscript{11}
- Antibodies decrease within 6 months after dose 3 of MenB-FHbp
- Development of bactericidal antibodies is dependent upon the particular strain of MenB

Safety of MenB-FHbp

- Data collected from the 7 clinical trials included results from >4,250 subjects aged 10–25 years who received at least 1 dose of MenB-FHbp\(^\text{17}\)
- No significant increased risk for serious adverse events from data collected
- Most common adverse reactions\(^\text{17,18}\)
  - Pain at the injection site (≥85% of subjects)
  - Fatigue (≥40%)
  - Headache (≥35%)
  - Myalgia (≥30%)
  - Chills (≥15%).


MenB-FHbp Contraindications

• Contraindications
  • Severe allergic reaction after a previous dose of Trumenba®
  • Pregnancy

4cMenB Immunogenicity Summary

- 5 clinical trials examined immunogenicity and safety: 3 randomized controlled, 1 randomized uncontrolled trial and 1 immunogenicity extension study
- 63-94% of adolescents demonstrated a composite hSBA response to 3 strains 1 month after vaccination with 2 doses
  - 63% among Canadian and Australian adolescents (95% CI--57%, 68%)
  - 88% among UK students (95% CI--82%, 93%)
  - 90-94% among Chilean students

# Immunogenicity Clinical Trials Summary of MenB-4C 1 Month Post Dose

<table>
<thead>
<tr>
<th>Study description</th>
<th>n</th>
<th>Age</th>
<th>4-fold hSBA response %</th>
<th>Composite hSBA Response %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled study in Chile(^1^9)</td>
<td>1631</td>
<td>11-17</td>
<td>90-94</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Randomized controlled study in the UK(^2^0)</td>
<td>2954</td>
<td>18-24</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Randomized uncontrolled in Australia and Canada 3 strains(^2^1)</td>
<td>344</td>
<td>11-17</td>
<td>39-99, depending on strain</td>
<td>63</td>
</tr>
</tbody>
</table>


MenB-4C Extension Summary

• Immunogenicity after 11 months, 66% hSBA titer of $\geq 1:4$ after 2 doses in UK students (CI—58%, 72%)\(^{11}\)
• 77-94% hSBA titer of $\geq 1:4$, 18-24 months after vaccination with 2 doses in Chilean students

Conclusion

• MenB vaccines provide short-term protection\textsuperscript{11}
• Modest decrease in antibodies through 24 months post dose 2 for MenB-4C
• Development of bactericidal antibodies is dependent upon the particular strain of MenB

Seroprevalence Survey After Mass Vaccination with 4cMenB at Princeton University

- Meningococcal outbreak in March 2013-March 2014
- 9 Cases, 1 fatality
- Outbreak strain had 2 MenB4C antigens, FHbp subfamily B and NHba
- Quantified immune response to 4CMenB among students 4 months post vaccination
- 4CMenB offered to all students, 607 enrolled
- Enrollment criteria: enrolled as an undergraduate or a graduate student, 18 years of age or older.
- Ineligible if they were ill or had a condition that prevented blood collection
- Participants provided a small blood sample and answered a questionnaire

Seroprevalence Survey After Mass Vaccination with 4cMenB at Princeton University

- Endpoints: hSBA titer of 4 or higher\(^{22}\)
- Within 6 months, 95% of eligible students had received at least one dose and 89% (499 students) had completed the two-dose series.
- 2 months after administering the 2\(^{nd}\) dose
  - 33.9% of those vaccinated had no evidence of antibody response, although no new reports of disease were reported

Safety of MenB-4C

- Data collected from 2,716 participants in 3 clinical trials\(^{23}\)
- Most common reactions included:
  - Pain at the injection site (83%)
  - Myalgia (%)
  - Erythema (%)
  - Fatigue (%)
  - Headache (%)
  - Induration (%)

\(^{23}\)Food and Drug Administration. Bexsero package insert.  
MenB-4C Contraindications

- Hypersensitivity including severe allergic reaction to any component of the vaccine\(^\text{23}\)
- Warnings and Precautions
  - Tip caps have natural rubber latex

ACIP Recommendations for MenB Vaccination

• Category A recommendation: For persons $\geq 10$ years old at increased risk for meningococcal disease$^{17}$
• Category B recommendation: Adolescents and young adults aged 16-23 may also be vaccinated to provide short term protection
• No product preference, but they are not interchangeable. The same vaccine must be used for all doses in series.
• 2 or 3 dose series of MenB-FHbp(Trumenba)
• 2 dose series MenB-4C (Bexsero)

Category B Recommendation Rationale

- Need for additional safety assessments\(^{11}\)
- More information needed on duration of protection
- High cost of vaccine
- Impact on nasopharyngeal carriage and herd protection not known
- Bexsero $320 for the series
- Trumenba $345 for 3-dose series
- Low burden of illness

MenB-FHbp

• Dose and schedule\textsuperscript{18}
  • 3-dose series: administered at 0, 1-2, and 6 months
  • 2-dose series: administered at 0 and 6 months

• Administration
  • Inspect for particulates or discoloration
  • Shake syringe vigorously until a homogeneous white mixture is obtained (do not use if vaccine cannot be resuspended)
  • Inject 0.5mL IM to the deltoid muscle of upper arm

MenB-4C

- **Dose and schedule**\(^{23}\)
  - 2 doses given at least one month apart

- **Administration**
  - Inspect for particulates or discoloration
  - Shake syringe vigorously until a homogeneous white mixture is obtained (do not use if vaccine cannot be resuspended)
  - Inject 0.5mL IM to the deltoid muscle of upper arm

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\(^{23}\)Food and Drug Administration. Bexsero package insert.  
Post-Test Questions

1. Which of the following is TRUE regarding herpes zoster (HZ)?
   a. HZ usually presents as a localized, unilateral, painful rash
   b. Herpes zoster is the infection that occurs after the initial exposure to VZV
   c. HZ is more common in adults younger than 50 years of age
   d. The symptoms of herpes zoster prodrome include severe GI upset
Post-Test Questions

2. Which of the following is TRUE regarding live zoster vaccine (Zostavax®)?
   a. Zostavax® is contraindicated in patients taking prednisone 50 mg PO once daily longterm
   b. Zostavax® should never be administered within 4 weeks of Pneumovax-23®
   c. Zostavax® is administered in the dose of 0.65 ml IM as a single dose
   d. Zostavax® can be administered to a patient who had cancer and has been in remission for 9 months
3. Which of the following is a side effect commonly associated with recombinant, adjuvanted zoster vaccine (Shingrix®)?
   a. Paresthesias
   b. Blurred vision
   c. Tachycardia
   d. Diarrhea
Post-Test Questions

4. Which of the following is the most common side effect associated with MenB-FHbp vaccine?
   a. Pain at the injection site
   b. Fatigue
   c. Headache
   d. Chills