Pneumococcal Disease in Adults 50+: A New Prevention Option
Program Agenda

• Explore the rationale for pneumococcal vaccination in the 50+ adult population in the United States
  • The impact of pneumococcal disease
  • Common serotypes causing invasive pneumococcal disease
  • The role of vaccination in antibiotic stewardship

• Review the background and clinical data for Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
  • Conjugate vaccine technology
  • Immunogenicity data for Prevnar 13®
  • Coadministration of Prevnar 13® with the inactivated influenza vaccine
INDICATIONS FOR PREVNAR 13®

- Prevnar 13® is a vaccine indicated for active immunization for the prevention of disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- In adults 50 years and older for pneumococcal pneumonia and invasive disease. Indication is based on immune responses
- In children 6 weeks through 5 years for invasive pneumococcal disease and otitis media (caused by 7 of the 13 serotypes only [4, 6B, 9V, 14, 18C, 19F, and 23F])

Limitations of Use and Effectiveness

- Prevnar 13® will only help protect against S pneumoniae serotypes in the vaccine
- Effectiveness when administered <5 years after pneumococcal polysaccharide vaccine is not known
IMPORTANT SAFETY INFORMATION

• Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid–containing vaccine is a contraindication

• Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response

• In adults, antibody responses to Prevnar 13® were diminished when given with inactivated Influenza Virus Vaccine

• In adults, the commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle or joint pain, decreased appetite, chills, or rash
IMPORTANT SAFETY INFORMATION

- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Vaccination of premature infants should be based on the infant’s medical status, and the potential benefits and risks
- In infants and toddlers, the most commonly reported serious adverse events were bronchiolitis (0.9%), gastroenteritis (0.9%), and pneumonia (0.9%)
- In infants and toddlers, the most commonly reported solicited adverse reactions were injection site tenderness, redness, or swelling, irritability, decreased appetite, decreased or increased sleep, and fever
Rationale for Vaccination in Adults 50+
What Is *Streptococcus pneumoniae*?

- The bacteria responsible for causing pneumococcal disease
- A leading cause of community-acquired pneumonia, meningitis, and bacteremia
- Exclusively human pathogen commonly carried in the nasopharynx
- More than 90 serotypes of *S. pneumoniae* have been identified

Incidence of Invasive Pneumococcal Disease*†

*S. pneumoniae isolated from a normally sterile site (e.g., blood, meninges) in residents of surveillance area in 2009.
†Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]) is indicated for use in children 6 weeks through 5 years of age (prior to the 6th birthday) and adults 50 years of age and older.

Major Clinical Syndromes of Pneumococcal Disease and Their Estimated Impact* on US Adults 50+

- 1700 Cases of Meningitis → ~19,000 Hospital Days
- 7000 Cases of Bacteremia/Sepsis → ~61,000 Hospital Days
- 140,000 Cases of Outpatient Pneumonia → ~220,000 and 51,000 Outpatient and Emergency Department Visits
- 302,000 Cases of Inpatient Pneumonia → More than: 321,000 Outpatient Visits†, 223,000 ED Visits, 1.7M Hospital Days

*Data are estimates derived from 2004-2005 statistics; assumptions based on published literature and expert opinion.
†No. of outpatient visits includes pre-admission and/or follow-up visits.
Most Common Serotypes*† Causing Invasive Pneumococcal Disease among Older Adults‡ in the United States

Serotypes 19A and 6A are among the most commonly antibiotic-resistant serotypes2,3

*Serotypes 6C and 22F are not included in Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
†Serotypes 6A and 6C are not included in PPSV.
‡≥65 years of age.
How Vaccination May Support Antibiotic Stewardship Efforts

Prevent Bacterial Infections → Less Antibiotic Use and Less Resistance

US Department of Health and Human Services.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM\textsubscript{197} Protein]): Overview
1881
Pneumococcal bacterium discovered

1911
The first large-scale trial of a crude whole-cell pneumococcal vaccine was conducted

1946
Two hexavalent vaccines were marketed

1977
14-valent vaccine was licensed

1983
23-valent polysaccharide vaccine (PPSV) was licensed

2000
7-valent conjugate vaccine (PCV7) was licensed for children

2010
13-valent conjugate vaccine (PCV13) was licensed for children

2011
PCV13 licensed for adults aged ≥50 yrs

References:
4. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
About Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein])

- Contains antigens from the capsular polysaccharide of 13 pneumococcal serotypes individually linked to nontoxic diphtheria CRM₁₉₇ protein
- No thimerosal
- Latex-free
- Single-dose prefilled syringe, 0.5 mL IM
  - May reduce dosing errors, product waste, and risk of contamination or transmission of infection
- 10 single-dose prefilled syringes per package
- Storage: refrigerate at +2° to +8°C (36° to 46°F)
- Preferred site of administration in adults is deltoid muscle
- Administered as a single dose to adults 50+

1. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
Rationale for Conjugation

- Pneumococcal capsular polysaccharide antigens are used in pneumococcal vaccines to induce serotype-specific antibody responses $^{1,2}$
  - Polysaccharides are T-cell independent antigens $^{1,2}$
- Conjugation of polysaccharides to a protein carrier enables a T-cell dependent response $^{1,3}$
  - Protein carrier specific T-cells facilitate maturation of the B-cell response $^{3,4}$

3. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
### Experience with Conjugate Vaccines in the United States

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Year Licensed</th>
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</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td>1987</td>
</tr>
<tr>
<td>Pneumococcal vaccine (7-valent)</td>
<td>2000</td>
</tr>
<tr>
<td>Meningococcal vaccine</td>
<td>2005</td>
</tr>
<tr>
<td>Pneumococcal vaccine (13-valent) Pediatrics</td>
<td>2010</td>
</tr>
</tbody>
</table>

US Approval Requirements for Adult Use

- For adults aged 50+, licensure of Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM$_{197}$ Protein]) was based on immunogenicity
  - There have been no controlled clinical trials in adults demonstrating a decrease in pneumococcal pneumonia or invasive disease after vaccination with Prevnar 13®
- Functional antibody responses, as a surrogate that is reasonably likely to predict clinical benefit, were measured using an opsonophagocytic activity (OPA) assay
- The functional antibody response generated by Prevnar 13® was compared to the functional antibody response induced by PPSV in subjects who were either PPSV-naïve or previously immunized with PPSV

FDA. VRBPAC Adult Indication Briefing Document for Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM$_{197}$ Protein]). November 16, 2011.
Study Subjects

Each study recruited the following:

- Healthy adults aged 50 and older
- Immunocompetent adults aged 50 and older with stable underlying conditions common in adults of this age that increase the risk of pneumococcal CAP and IPD:
  - Chronic cardiovascular disease
  - Chronic pulmonary disease
  - Renal disorders
  - Diabetes mellitus
  - Chronic liver disease, including alcoholic liver disease and alcoholism

CAP = community-acquired pneumonia; IPD = invasive pneumococcal disease.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM\textsubscript{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]): Functional Antibody Response in Pneumococcal Vaccine–Naïve Adults*

*Noninferiority study.
†Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel and subjects were blinded.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Study Design

Active-controlled, modified† double-blind clinical trial (noninferiority study in PPSV-unvaccinated adults) of Prevnar 13® in the United States:

- PPSV-unvaccinated adults aged 60-64 years received PPSV: n = 367-402
- PPSV-unvaccinated adults aged 60-64 years received Prevnar 13®: n = 359-404
- Adults aged 50-59 years received 1 dose of Prevnar 13® (open label): n = 350-384
Study Design (cont’d)

• Functional antibody response was measured using the opsonophagocytic assay (OPA), which quantifies the ability of immune sera to mediate the killing of *S. pneumoniae* by phagocytic cells
  
  • Serotype-specific OPA geometric mean titers (GMTs) measured 1 month after each vaccination were calculated
  
  • Predetermined noninferiority threshold between antibody responses was defined as the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) greater than 0.5
  
  • Response to serotype 6A, which is contained in Prevnar 13® but not in PPSV, was assessed by the proportion of subjects in each group who demonstrated a 4-fold increase in the specific OPA titer above pre-immunization levels

*Noninferiority study.  
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]): Demonstrated Functional Antibody Response in Pneumococcal Vaccine-Naïve Adults

Primary End Point Determined Noninferiority of Immune Responses to Prevnar 13® Compared with PPSV for the 12 Shared Serotypes plus Serotype 6A

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
Prescribing Information, Wyeth Pharmaceuticals Inc.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM$_{197}$ Protein]): Demonstrated Functional Antibody Response in Pneumococcal Vaccine-Naïve Adults (cont’d)

Secondary End Point: Statistically Significantly Higher Immune Response to PCV 13 for Some Shared Serotypes When Compared with Response to PPSV

- There have been no studies demonstrating the relationship between these immune responses and reductions in pneumococcal pneumonia and invasive disease.
Study Design

Active-controlled, modified† double-blind clinical trial (noninferiority study in PPSV-prevaccinated adults) of Prevnar 13® in the United States:

Subjects were previously vaccinated with PPSV ≥5 years prior per previous Centers for Disease Control and Prevention (CDC) recommendations for adults aged ≥65

*Noninferiority study.
†Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel and subjects were blinded.
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM$_{197}$ Protein]): Functional Antibody Response in Adults Previously Vaccinated with PPSV*

Study Design (cont’d)

- Functional antibody response was measured using the OPA, which quantifies the ability of immune sera to mediate the killing of *S. pneumoniae* by phagocytic cells
  - Serotype-specific OPA geometric mean titers (GMTs) measured 1 month after each vaccination were calculated
  - Predetermined noninferiority threshold between antibody responses was defined as the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) greater than 0.5
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Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM$_{197}$ Protein]): Demonstrated Functional Antibody Response in Adults Previously Vaccinated with PPSV
Secondary End Point: Statistically Significantly Higher Immune Response to PCV 13 for Some Shared Serotypes When Compared with Response to PPSV

- There have been no studies demonstrating the relationship between these immune responses and reductions in pneumococcal pneumonia and invasive disease.
• In PPSV unvaccinated adults and PPSV previously vaccinated adults:
  • The commonly reported local adverse reactions were redness, swelling and pain at the injection site, or limitation of arm movement
  • The commonly reported systemic adverse reactions were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain
• Prevnar 13® can be coadministered with inactivated influenza virus vaccine (TIV) in adults aged 50 years and older
  • Frequencies of local reactions within 14 days post vaccination in adults aged 50-59 years and in adults aged ≥65 years were similar after Prevnar 13® was administered with TIV compared to Prevnar 13® administered alone, with the exception of mild redness at the injection site, which was increased when Prevnar 13® was administered concomitantly with TIV
• When TIV and Prevnar 13® were administered together and the immune response was compared with the immune response to each vaccine given alone:
  • Antibody responses to Prevnar 13® were diminished
  • Noninferior responses to all 3 TIV strains were observed in adults 50-59 years of age
  • In adults ≥65 years, noninferiority was demonstrated for A/H1N1 and B-strains, but not for H3N2

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Summary

• Pneumococcal disease is a serious disease that impacts adults 50+
• Streptococcus pneumoniae can be resistant to antibiotics which makes prevention even more important
• Prevnar 13® was approved by the FDA on December 30, 2011 for use in adults aged 50 years and older to help prevent pneumococcal pneumonia and invasive disease caused by the 13 serotypes in the vaccine
• In clinical trials, Prevnar 13® generated a functional antibody response that was non-inferior to PPSV in both pneumococcal vaccine-naïve adults and those previously immunized with PPSV
• Prevnar 13® can be coadministered with TIV in adults 50+

For more information, visit www.prevnar13adulthcp.com