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 CRM_{197} Protein])
  - Conjugate vaccine technology
  - Immunogenicity data for Prevnar 13®
  - Coadministration of Prevnar 13® with the inactivated influenza vaccine

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Indications

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

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Important Safety Information

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

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Important Safety Information

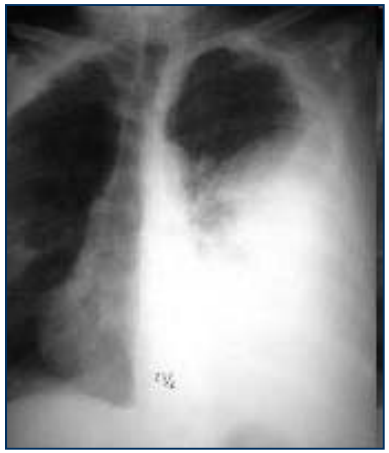
IMPORTANT SAFETY INFORMATION

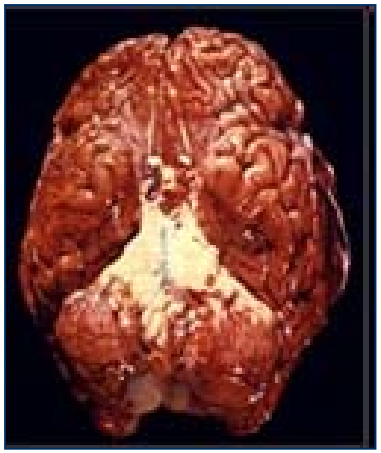
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Vaccination of premature infants should be based on the infant's medical status, and the potential benefits and risks
- In infants and toddlers, the most commonly reported serious adverse events were bronchiolitis (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?*

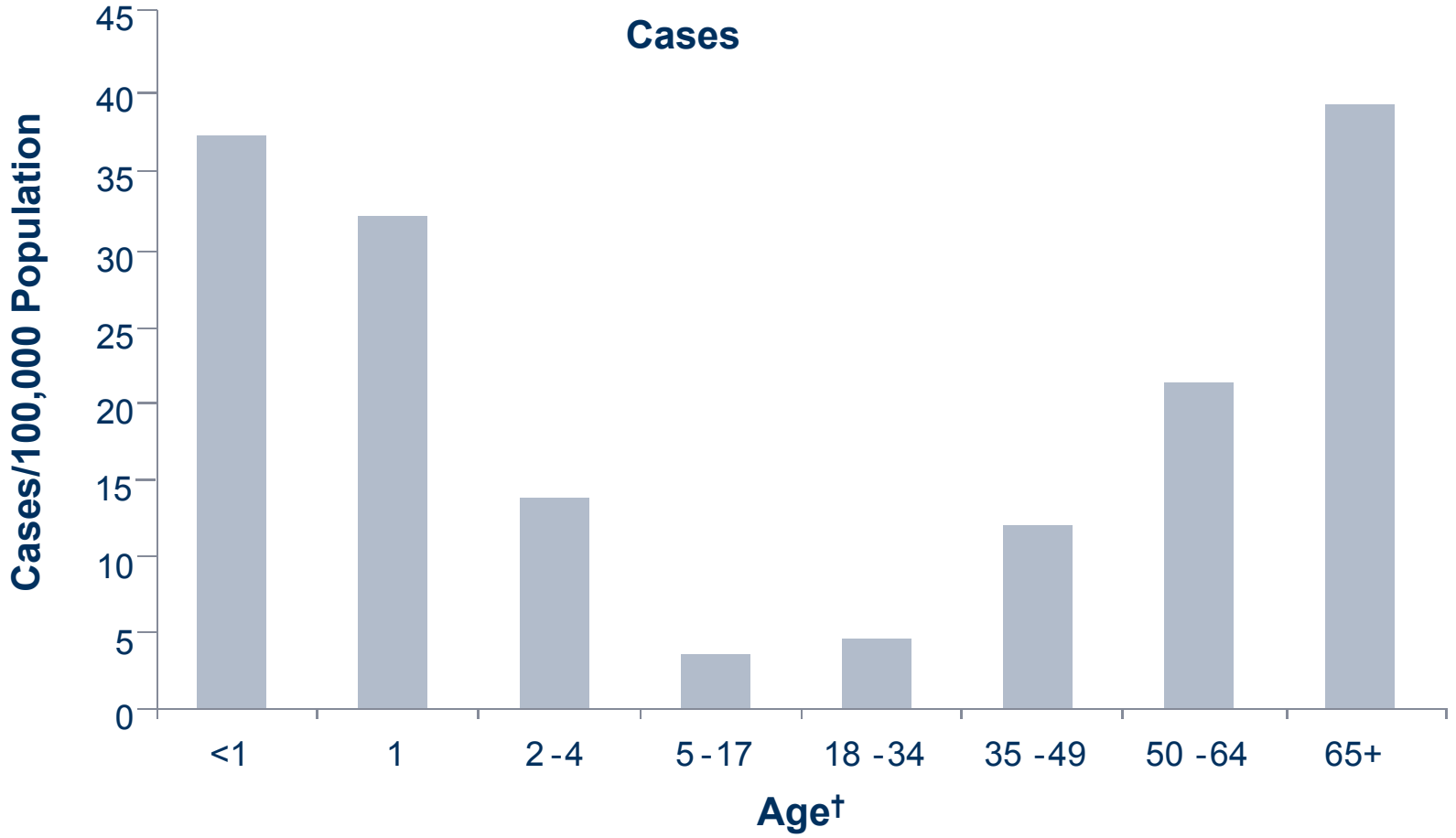
- The bacteria responsible for causing pneumococcal disease
- A leading cause of community-acquired pneumonia, meningitis, and bacteremia
- Exclusively human pathogen commonly carried in the nasopharynx
- More than 90 serotypes of *S. pneumoniae* have been identified





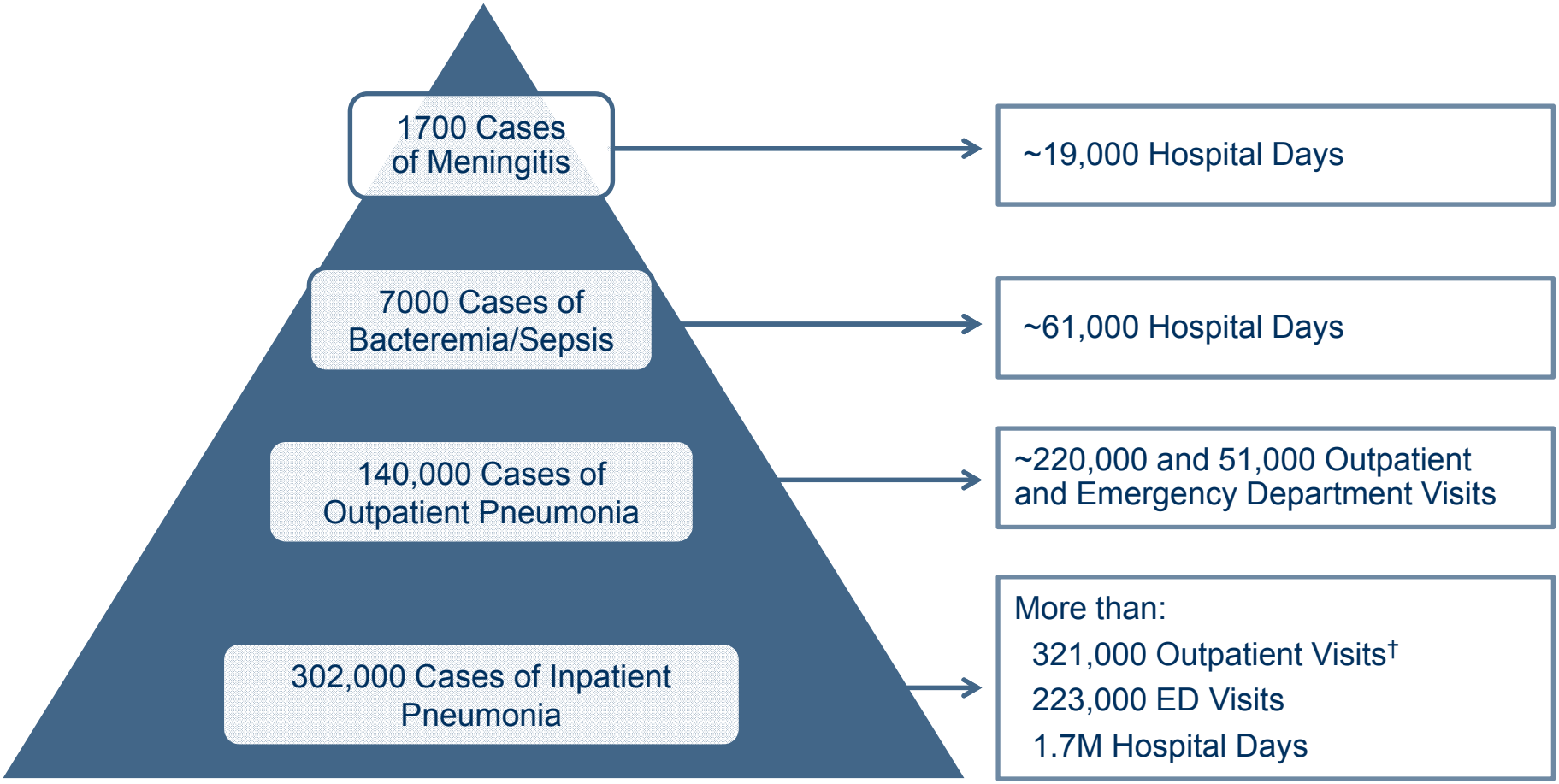
CDC. Pneumococcal disease. In: Atkinson W, Wolfe S, Hamborsky J, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* 12th ed. Washington, DC: Public Health Foundation; 2011:233-248.

Incidence of Invasive Pneumococcal Disease*†



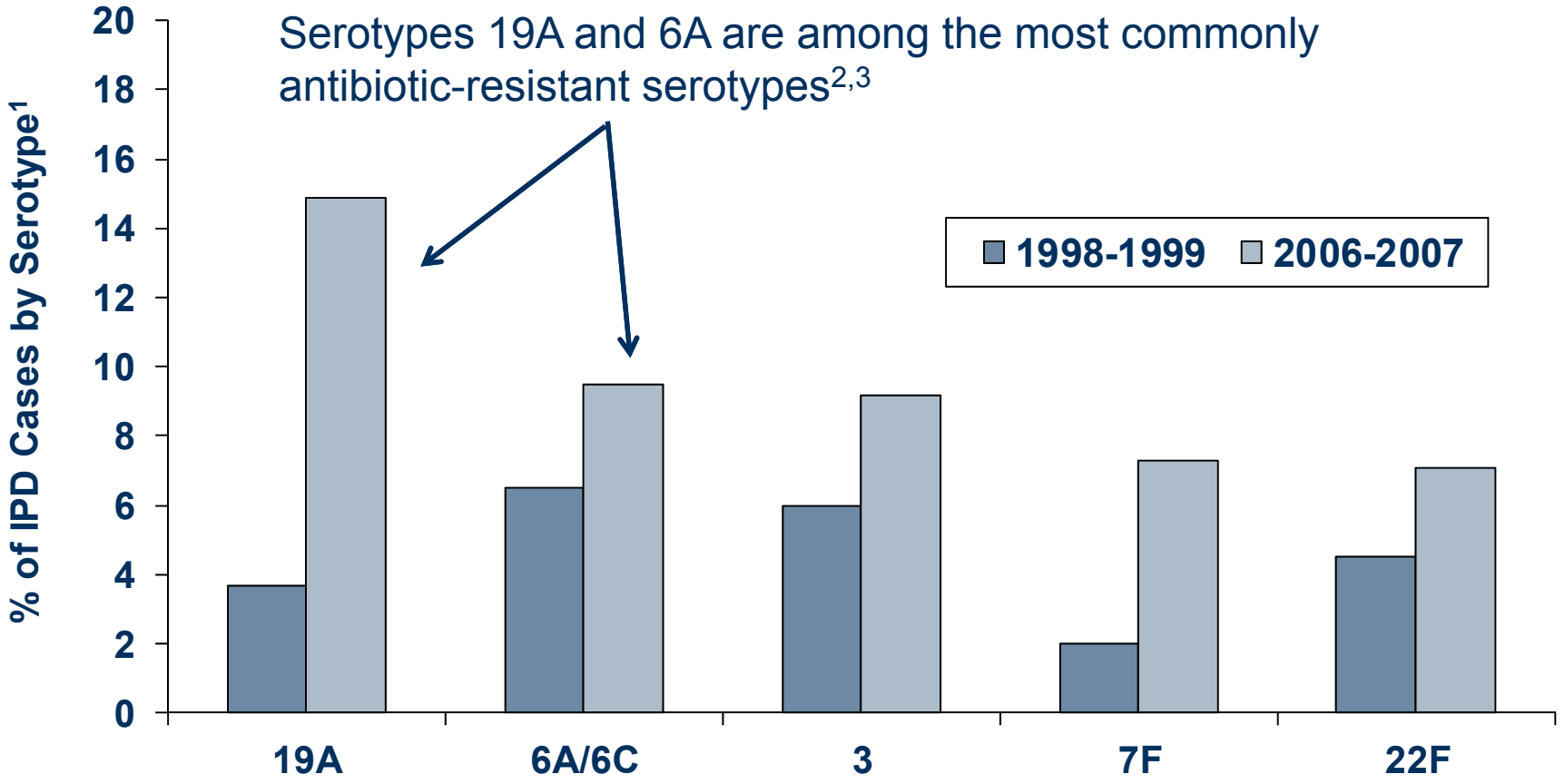
**S. pneumoniae* isolated from a normally sterile site (eg, blood, meninges) in residents of surveillance area in 2009.
†Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) is indicated for use in children 6 weeks through 5 years of age (prior to the 6th birthday) and adults 50 years of age and older.
Adapted from CDC. Active Bacterial Core Surveillance. 2009. http://www.cdc.gov/abcs/reports-findings/survreports/spneu09.html. Accessed February 21, 2011.

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



*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.
Huang SS, et al. *Vaccine.* 2011;29:3398-3412.

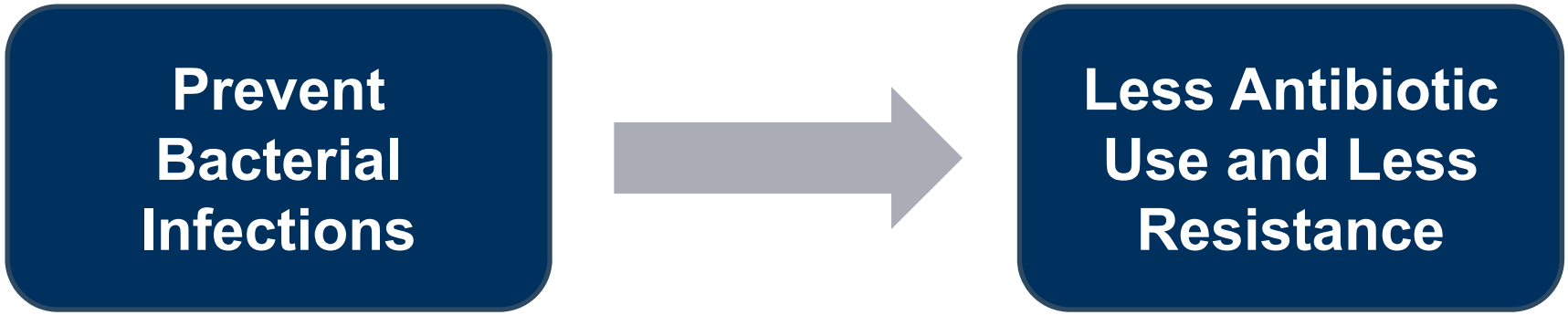
Most Common Serotypes*† Causing Invasive Pneumococcal Disease among Older Adults‡ in the United States



*Serotypes 6C and 22F are not included in Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])
†Serotypes 6A and 6C are not included in PPSV.
‡≥65 years of age.

1. Pilishvili T, et al. *J Infect Dis*. 2010;201:32-41.
2. Moore MR, et al. *J Infect Dis*. 2008;197:1016-1027.
3. Richter SS, et al. *Clin Infect Dis*. 2009;48:e23-e33.

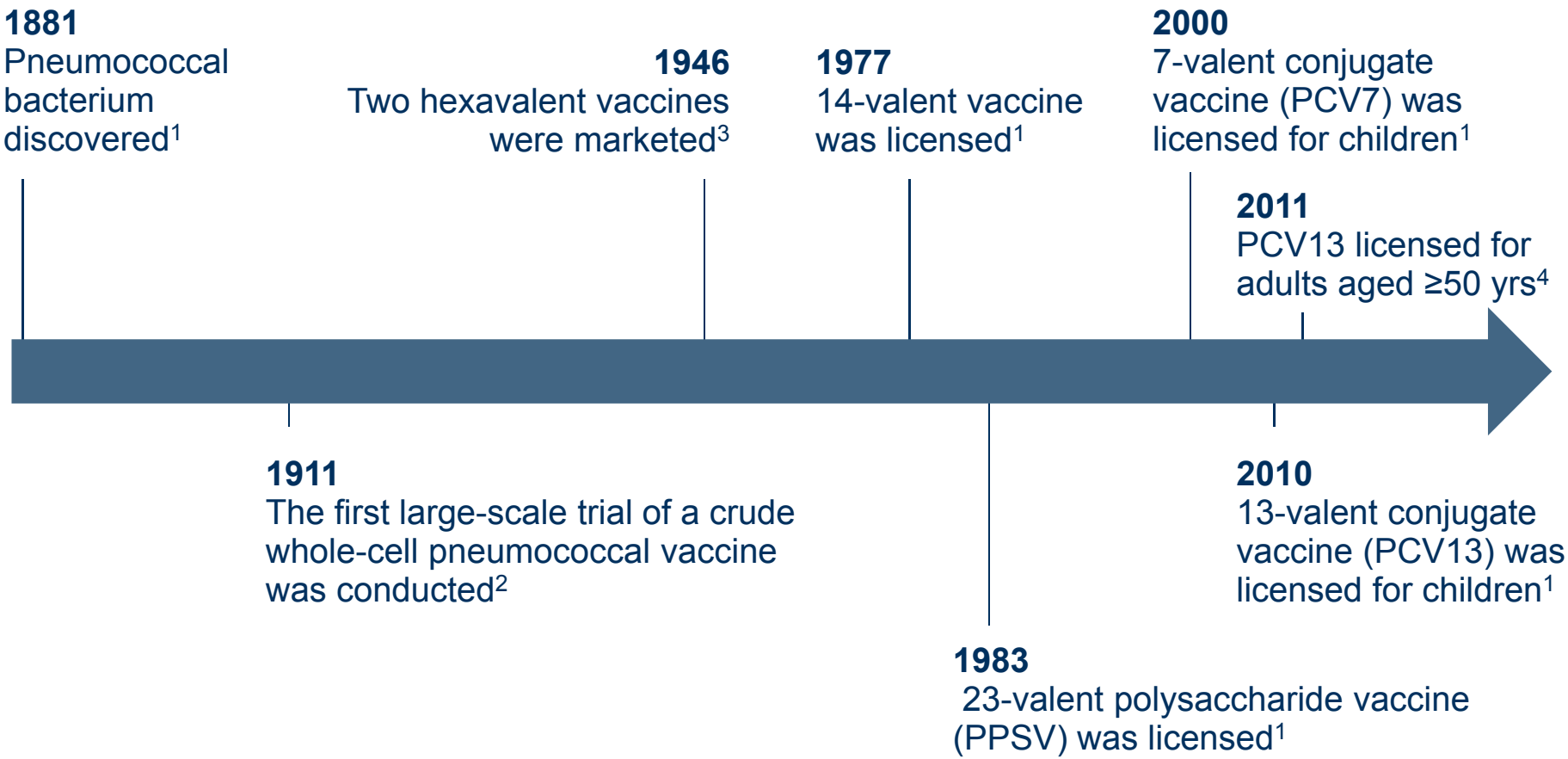
How Vaccination May Support Antibiotic Stewardship Efforts



US Department of Health and Human Services.
http://www.hhs.gov/asl/testify/2009/07/t20090713a.html. Accessed May 24, 2011.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Overview

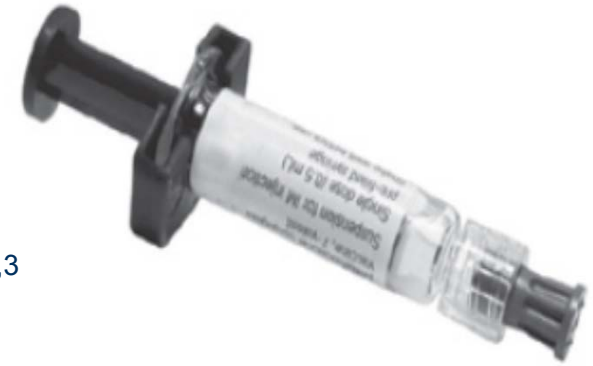
History of Pneumococcal Vaccines Licensed and Recommended in the United States



1. CDC. Pneumococcal disease. In: *Epidemiology and Prevention of Vaccine-Preventable Diseases.* 12th ed. Washington DC: Public Health Foundation, 2011.
2. Williams C, et al. *J Infect*. 2008;56:13-19.
3. Targonski PV, et al. *Cleve Clin J Med*. 2007;74:401-413.
4. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

About Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])

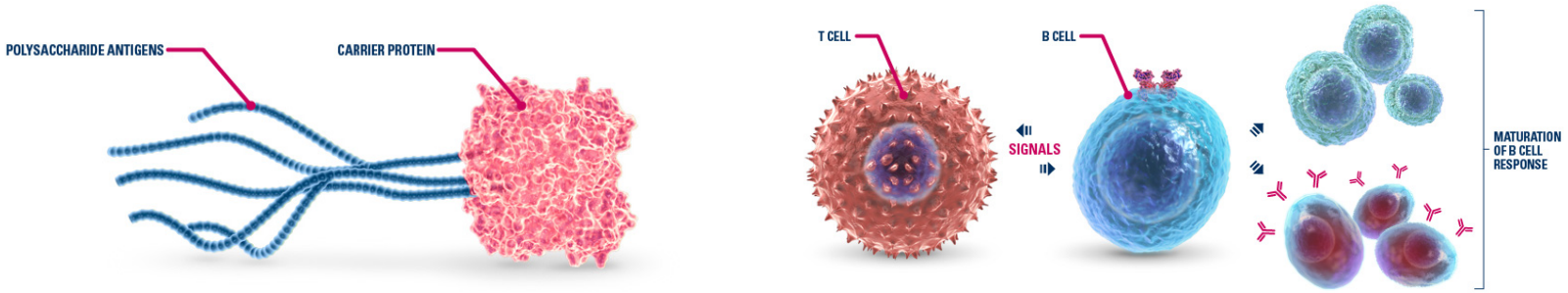
- Contains antigens from the capsular polysaccharide of 13 pneumococcal serotypes individually linked to nontoxic diphtheria CRM_{197} protein[1]
- No thimerosal[1]
- Latex-free[1]
- Single-dose prefilled syringe, 0.5 mL IM[1]
  - May reduce dosing errors,[1] product waste,[2] and risk of contamination or transmission of infection[2,3]
- 10 single-dose prefilled syringes per package[1]
- Storage: refrigerate at +2° to +8°C (36° to 46°F)[1]
- Preferred site of administration in adults is deltoid muscle[1]
- Administered as a single dose to adults 50+[1]



1. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
2. Drain PK, et al. *Bull World Health Org*. 2003;81:726-731.
3. Gosbell IB, et al. *Vaccine*. 2010;28:6556-6561.

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]



1. Siegrist CA. Vaccine immunology. Section 1: General aspects of vaccination. http://www.who.int/immunization/documents/Elsevier_Vaccine_immunology.pdf. Accessed January 13, 2011.
2. de Roux A, et al. *Clin Infect Dis*. 2008;46:1015.
3. Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.
4. Pollard AJ, et al. *Nat Rev Immunol*. 2009;9:213-220.

Experience with Conjugate Vaccines in the United States

Vaccine	Year Licensed
Haemophilus influenzae type b	1987
Pneumococcal vaccine (7-valent)	2000
Meningococcal vaccine	2005
Pneumococcal vaccine (13-valent) Pediatrics	2010

CDC. Principles of vaccination. In: Atkinson W, Wolfe S, Hamborsky J, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Washington, DC: Public Health Foundation; 2011:1-8.

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.

Inclusion Criteria for Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Clinical Trials: Overview

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_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Functional Antibody Response in Pneumococcal Vaccine–Naïve Adults*

Study Design

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

PPSV: n = 367-402

Prevnar 13®: n = 359-404

Prevnar 13®: n = 350-384

*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]) Prescribing Information, Wyeth Pharmaceuticals Inc.

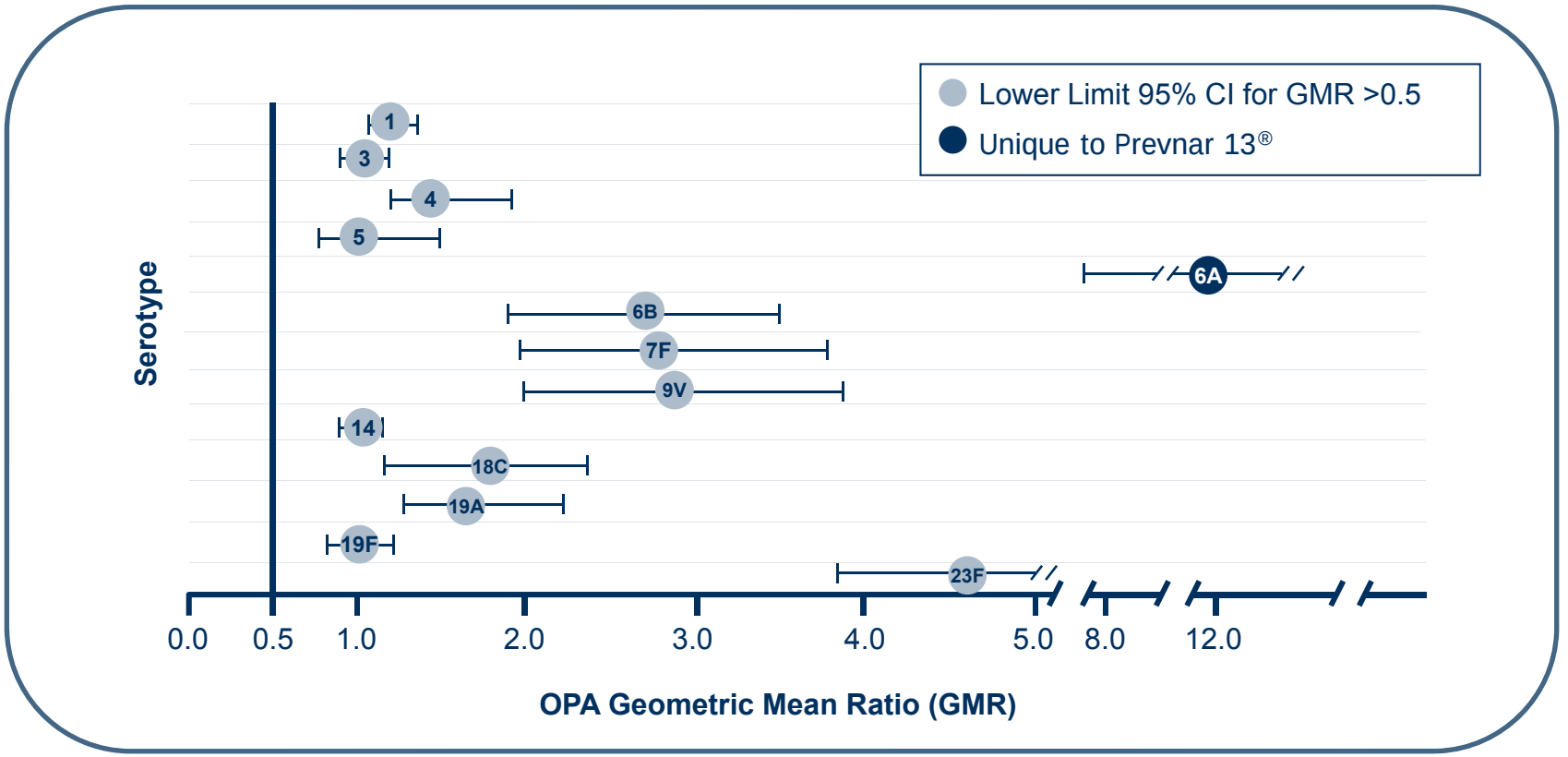
Study Design (cont'd)

- 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 CRM_{197} 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

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



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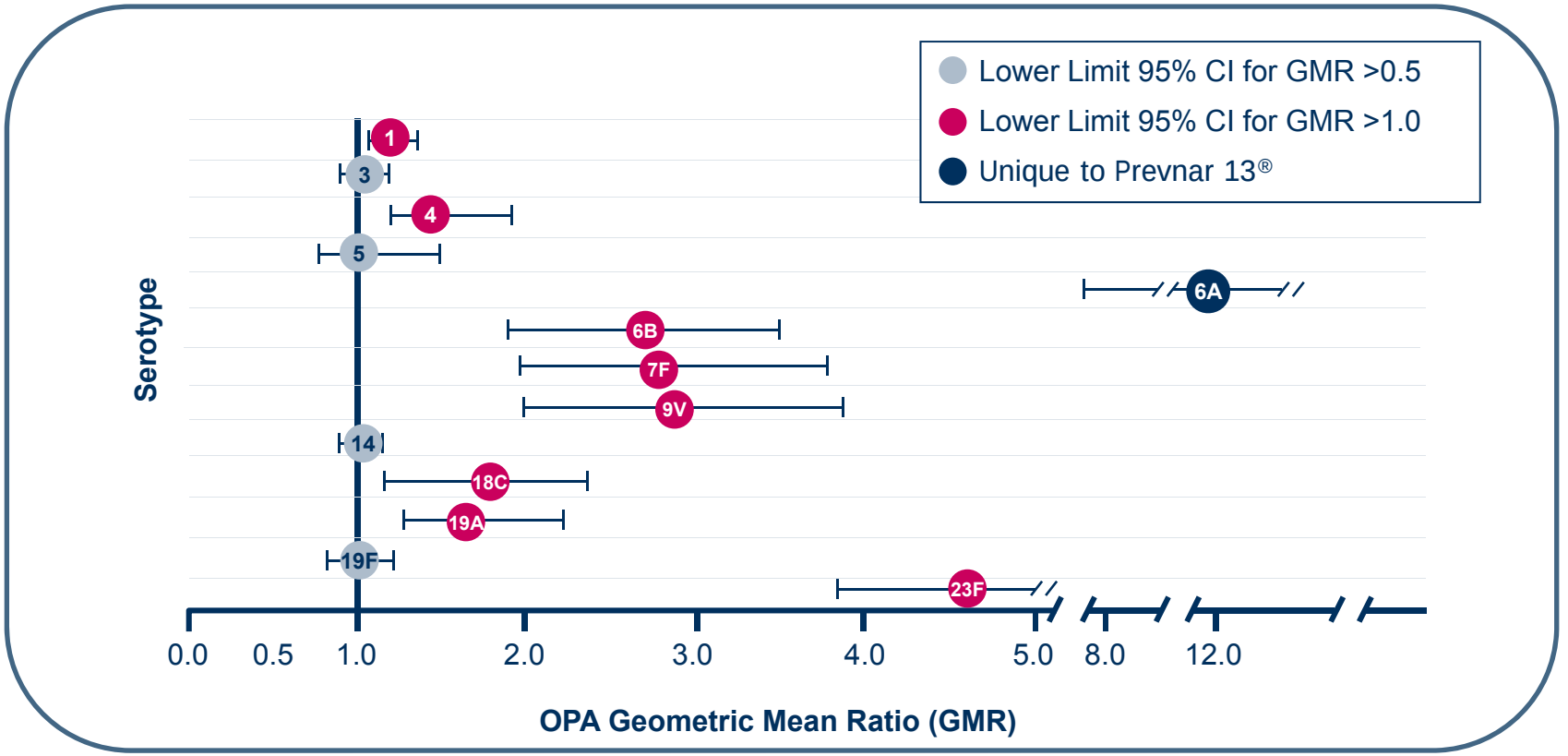
Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Demonstrated Functional Antibody Response in Pneumococcal Vaccine-Naïve Adults (cont'd)

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



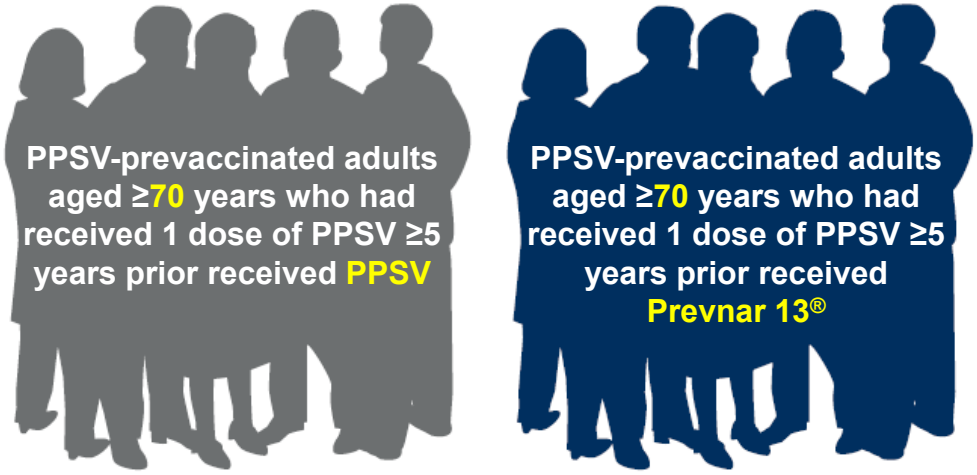
- There have been no studies demonstrating the relationship between these immune responses and reductions in pneumococcal pneumonia and invasive disease.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Functional Antibody Response in Adults Previously Vaccinated with PPSV*

Study Design

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



PPSV: n = 395-445

Prevnar 13®: n = 400-426

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]) Prescribing Information, Wyeth Pharmaceuticals Inc.

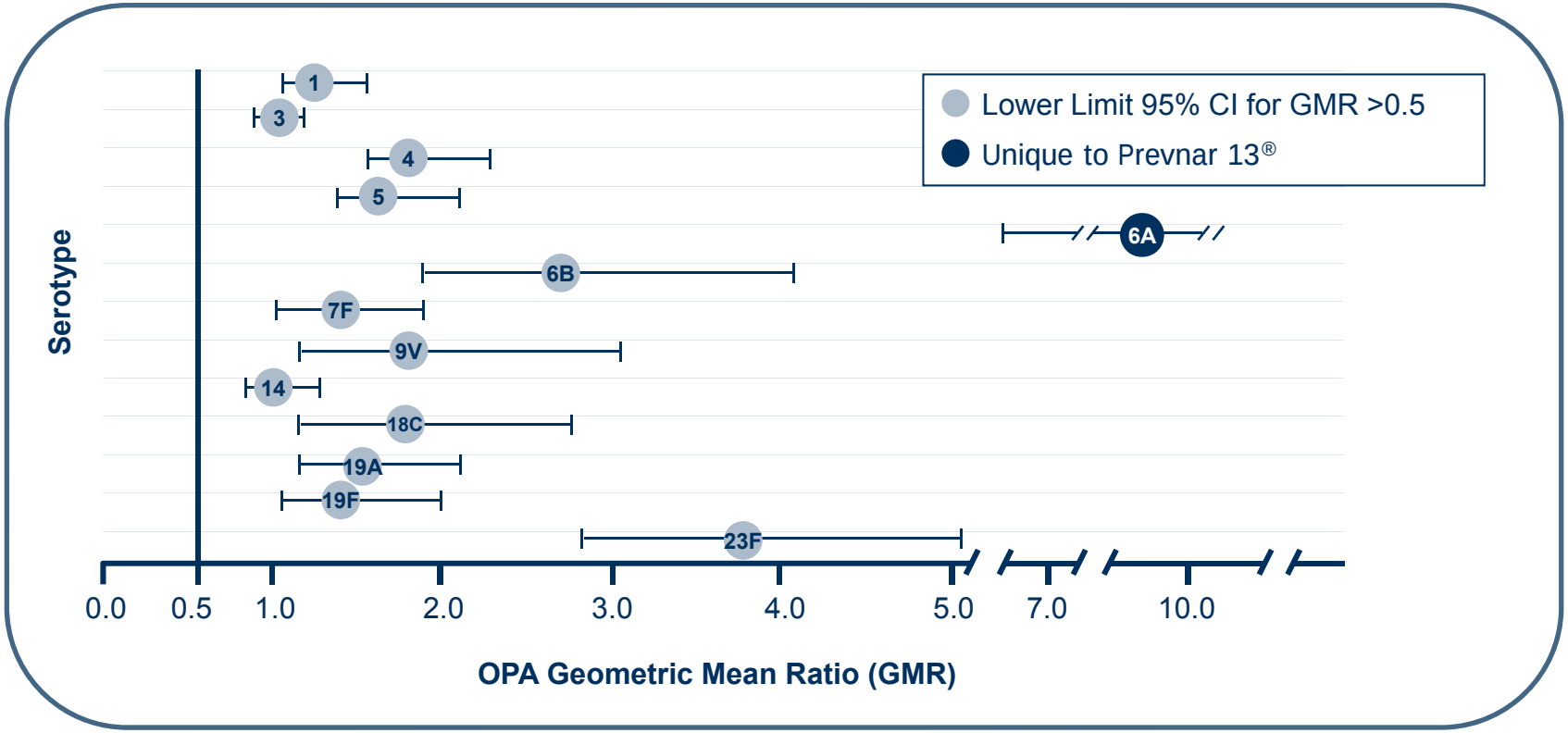
Study Design (cont'd)

- 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
  - 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 CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Demonstrated Functional Antibody Response in Adults Previously Vaccinated with PPSV

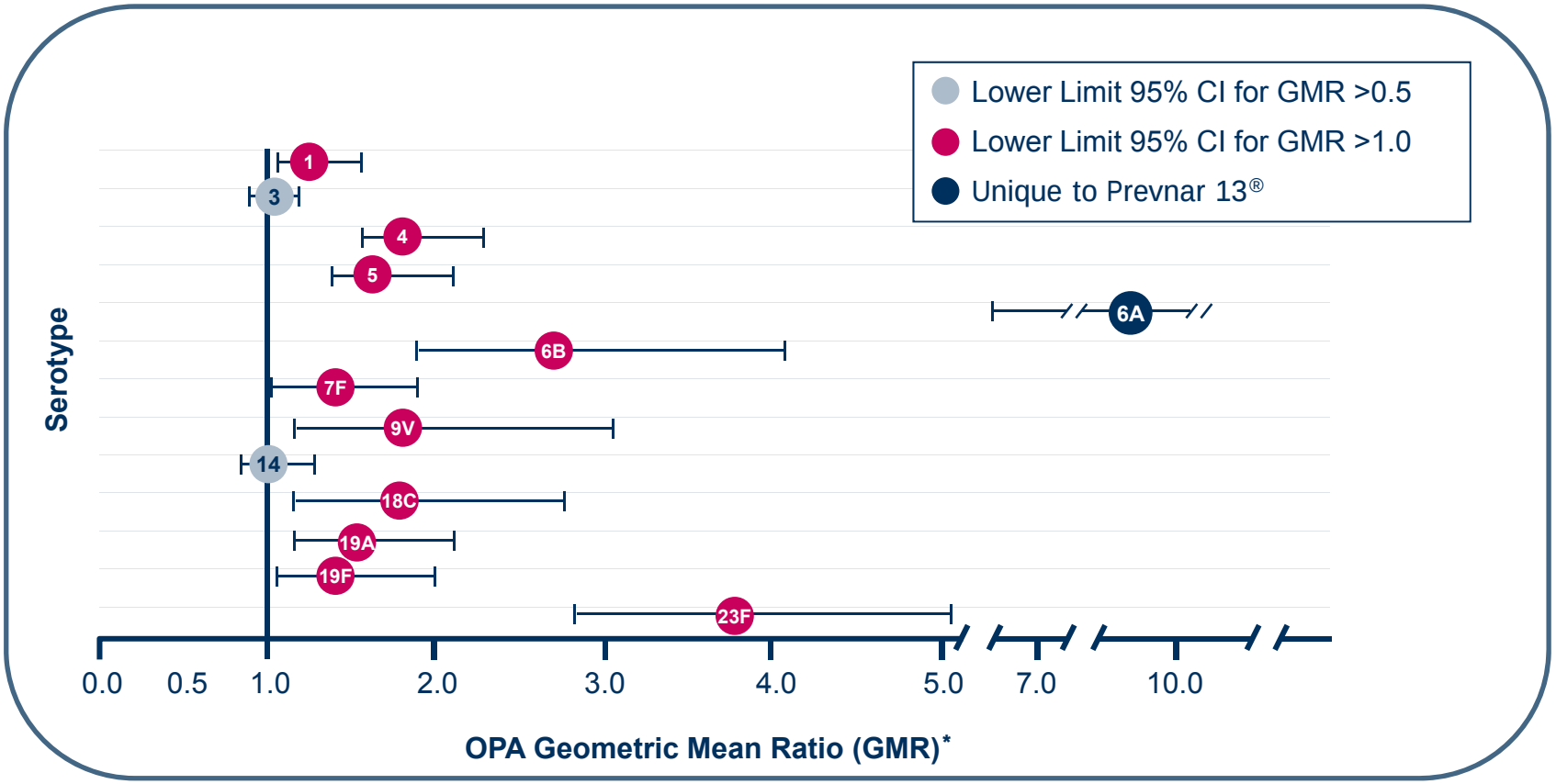
Primary End Point Determined Noninferiority of Immune Responses to Prevnar 13® Compared with PPSV for the 12 Shared Serotypes plus Serotype 6A



Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Demonstrated Functional Antibody Response in Adults Previously Vaccinated with PPSV (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.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Safety and Tolerability Summary

- 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

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]) Prescribing Information, Wyeth Pharmaceuticals Inc.

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Concomitant Administration with the Influenza Vaccine

- 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
- Prevnar 13® can be coadministered with inactivated influenza virus vaccine (TIV) in adults aged 50 years and older

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- 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

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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

Prevnar 13® (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]): Important Safety Information

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

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