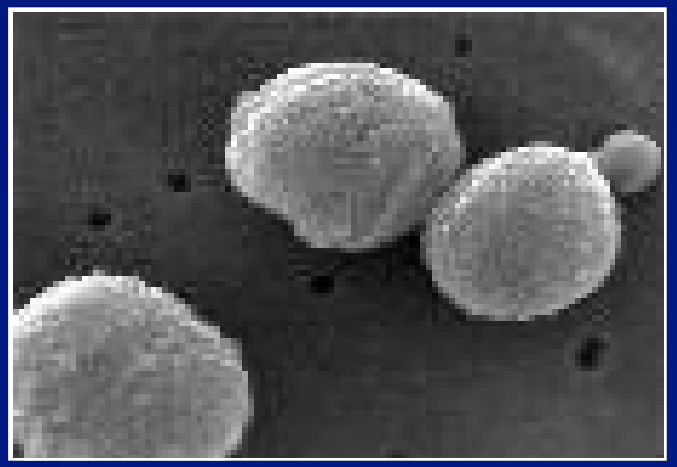
# Pneumococcal Disease and Pneumococcal Vaccines

National Center for Immunization & Respiratory Diseases
Immunization Services Division

# Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other types of pneumonia until the development of the Gram stain in 1884
- More than 80 serotypes described by 1940
- First U.S. licensed vaccine in 1977

# *Streptococcus pneumoniae*



- Gram-positive bacteria
- 92 known serotypes
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective
- Limited cross-reactivity

# Pneumococcal Disease

- Second most common cause of vaccine-preventable death in the U.S.
- Major clinical syndromes
  - Pneumonia
  - Bacteremia
  - Meningitis

# Pneumococcal Disease

- **Pneumonia**
  - Estimated 400,000 hospitalizations/year in the United States
  - Case-fatality rate (CFR) 5%-7%, higher in the elderly
- **Bacteremia**
  - About 12,000 cases without pneumonia per year in the United States
  - CFR: 20%, can be much higher (60%) in the elderly
- **Meningitis**
  - About 3,000-6000 cases per year in the United States
  - CFR 8% in children, 22% in adults
  - Neurologic sequelae common among survivors

CDC data at http://www.cdc.gov/pneumococcal/clinicians/clinical-features.html

# Risk Factors for Invasive Pneumococcal Disease

- Children 2 years of age and younger
- Persons 65 years of age and older
- Underlying medical conditions, including CSF leak
- Cigarette smoking (adults 19 years and older)
- Cochlear implant

# Other Conditions that Increase Risk for Invasive Pneumococcal Disease

- Decreased immune function
- Asplenia (functional or anatomic)

# Burden of Pneumococcal Disease in Children (prior to routine use of PCV)*

| Syndrome | Cases |
|---|---|
| Bacteremia | 13,000 |
| Meningitis | 700 |
| Death | 200 |
| Otitis media | 5 million |

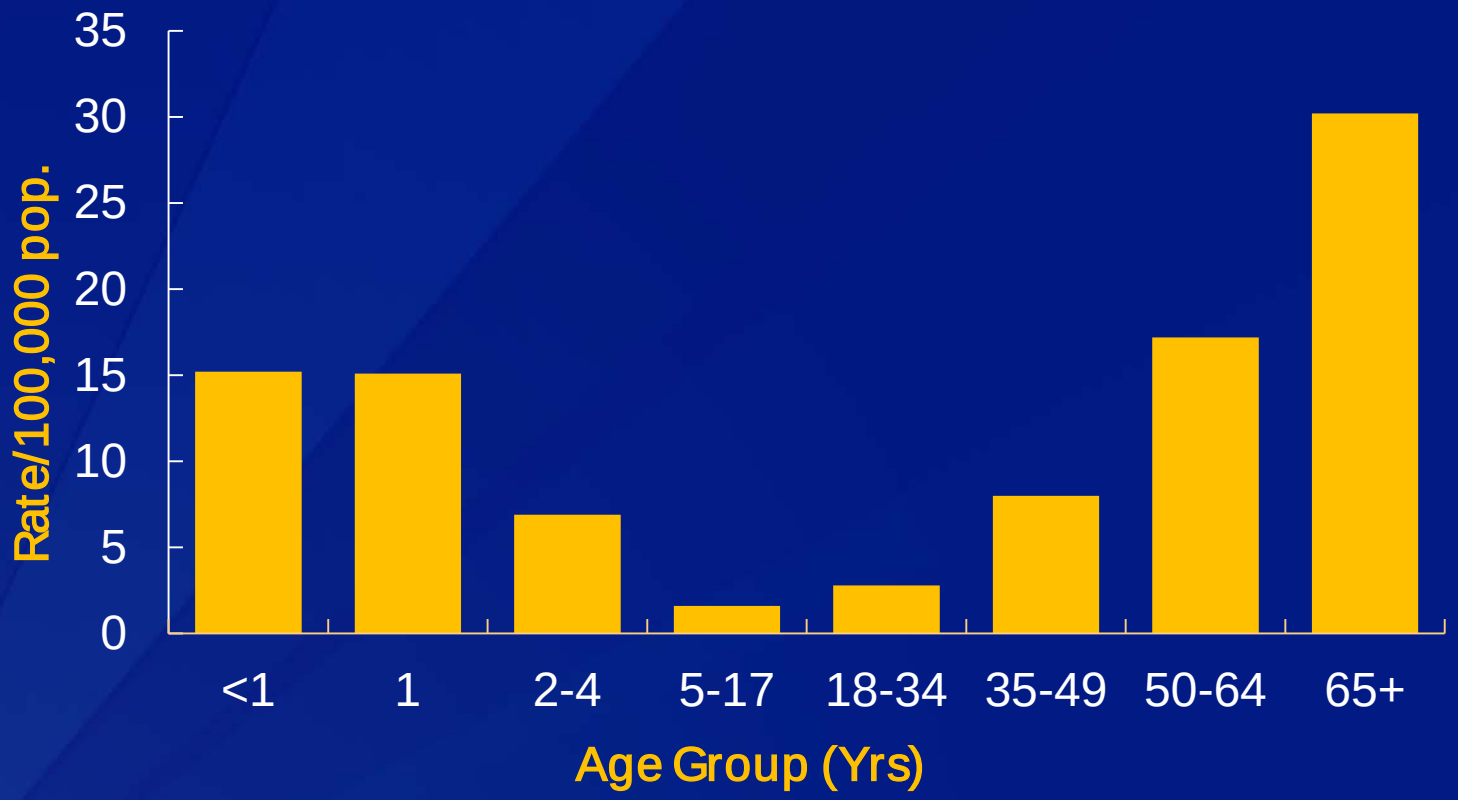
# Children at Increased Risk of Invasive Pneumococcal Disease

- Functional or anatomic asplenia, especially sickle cell disease
- Immune compromise, including HIV infection
- Child care attendance
- Alaska Native, certain American Indian (Navajo and White Mountain Apache), and African American
- Cochlear implant
- CSF Leak

# Pneumococcal Disease Epidemiology

| | |
|---|---|
| Reservoir | Human carriers |
| Transmission | Respiratory and autoinoculation |
| Temporal pattern | Winter and early spring |
| Communicability | Unknown; probably as long as organism in respiratory secretions |

# Invasive Pneumococcal Disease Incidence by Age Group – 2013*




*CDC ABC's report:
http://www.cdc.gov/abcs/reports-findings/survreports/spneu13.html

# Invasive Pneumococcal Disease (IPD) in the United States

| | Rate per 100,000 children younger than 5 years | |
|---|---|---|
| | Before vaccine | 2008 |
| All IPD | 99 | 21 |
| PCV7 serotypes | 82 | 0.2 |

Source: Active Bacterial Core Surveillance/EIP Network

# Pneumococcal Vaccines

- **1977** 14-valent polysaccharide vaccine licensed
- **1983** 23-valent polysaccharide vaccine licensed (PPSV23)
- **2000** 7-valent polysaccharide conjugate vaccine licensed (PCV7)
- **2010** 13-valent polysaccharide conjugate vaccine licensed (PCV13)

# Pneumococcal Polysaccharide Vaccine (PPSV23) - Characteristics

- Purified capsular polysaccharide antigen from 23 types of pneumococcus
- Not effective in children younger than 2 years

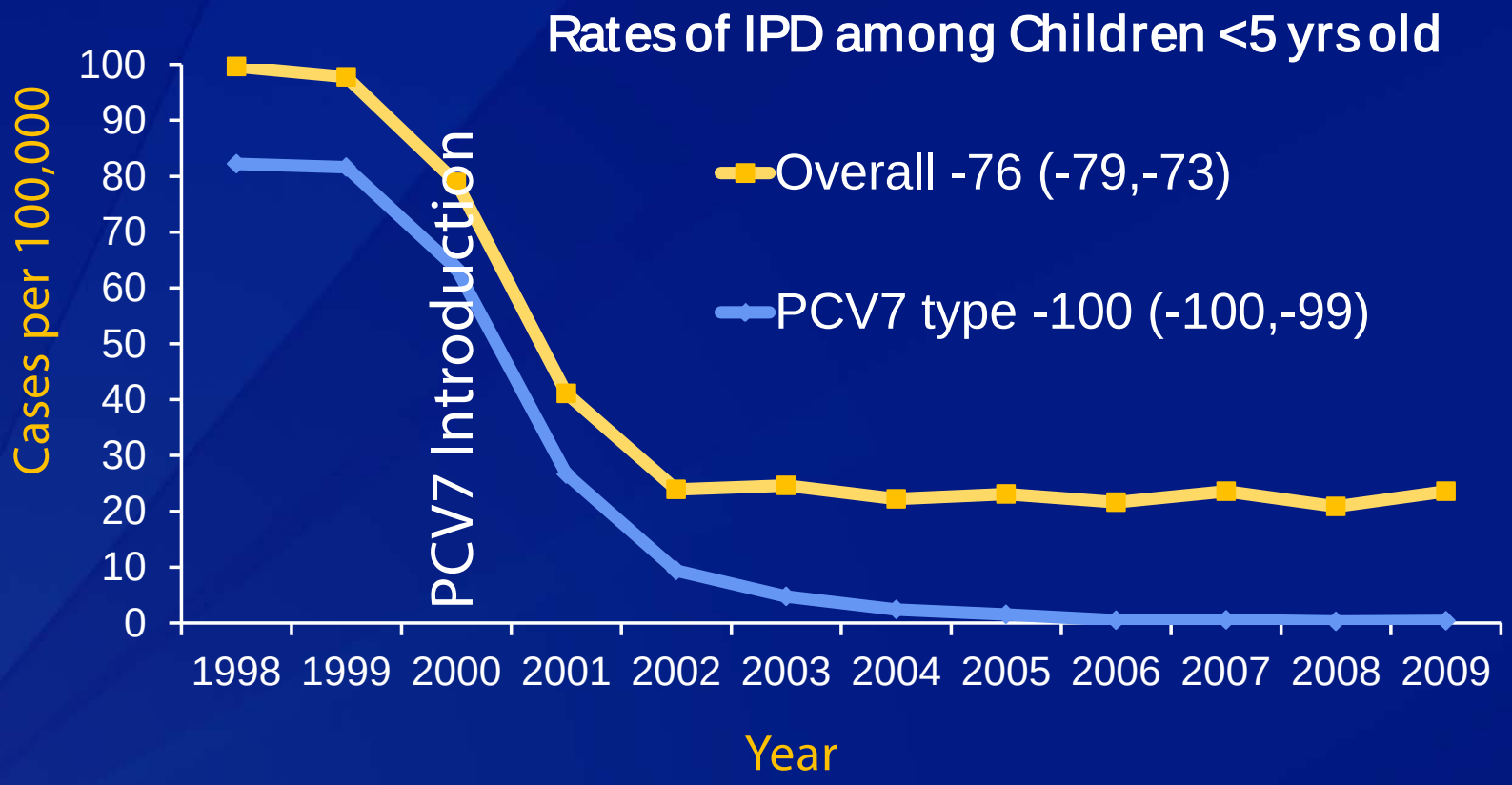
# Pneumococcal Conjugate Vaccine (PCV13) - Characteristics

- Contains the same serotypes of *S. pneumoniae* as PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A conjugated to nontoxic diphtheria $CRM_{197}$ carrier protein
- Approval based on demonstration of immunologic non-inferiority to PCV7 rather than clinical efficacy

*MMWR* 2010;59(No. 9):258-61

# PCV7 introduction Among U.S. Children and its Impact on Invasive Pneumococcal Disease

- PCV7 introduced into routine schedule 2000




Moore, IDSA, 2009 and CDC Unpublished

# Pneumococcal Conjugate Vaccine (PCV13) Children

- In 2008, 61% of invasive pneumococcal disease cases among children younger than 5 years were attributable to the serotypes included in PCV13

# Pneumococcal Conjugate Vaccine (PCV13) Adults

- In 2013, 20%-25% of invasive pneumococcal disease cases among adults 65 years old and older were attributable to PCV13 serotypes
- Ten percent of community acquired pneumonia in adults due to PCV13 serotypes - Pfizer urine studies

# Estimating cases potentially preventable annually among adults 65 years or older

| Outcome (PCV13 type) | 2015<br>20% reduction due to herd effects*<br>PCV13 direct effects**<br>Coverage 10% (5%-30%) | 2019<br>86% reduction due to herd effects*<br>PCV13 direct effects**<br>Coverage 30% (20%-60%) |
|---|---|---|
| IPD | 160 (80-480) | 80 (50-170) |
| Inpatient CAP | 2,030 (1,020-6,090) | 1,070 (700 -2,130) |
| Outpatient CAP | 2,970 (1,480-8,900)) | 1,560 (1,040 – 3,120) |
| Total CAP | 5,000 (2,500-14,990) | 2,630 (1,740 – 5,250) |

*Based on post-PCV7 reductions observed between 2003 and 2009
**Assume PCV13 VE =75% (IPD) and 45% (CAP)

# Pneumococcal Polysaccharide Vaccine (PPSV23) – Immunogenicity/Effectiveness

- Most estimates range between 60%-70% effective against invasive disease among immunocompetent older persons and adults with underlying illnesses
- Effectiveness among immunocompromised or very old persons not demonstrated

# Pneumococcal Conjugate Vaccine (PCV13) Immunogenicity/Efficacy

- Highly immunogenic in infants and young children, including those with high-risk medical conditions
- PCV7 was 97% effective against invasive disease caused by vaccine serotypes (presumably PCV13 as well)

# ACIP 2014: New Evidence Supporting PCV13 use among adults, CAPiTA results

| Study/population | Endpoint | Vaccine Efficacy (95% CI) |
|---|---|---|
| CAPITA ~85,000 Adults 65+ Netherlands | PCV13-serotype IPD | 75% (41%, 91%) |
| | PCV13-serotype non-bacteremic pneumonia | 45% (14%, 65%) |

CAPITA, ACIP June 2014

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | December 10, 2010 / Vol. 59 / No. RR-11

# Prevention of Pneumococcal Disease Among Infants and Children — Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine

## Recommendations of the Advisory Committee on Immunization Practices (ACIP)

# PCV13 Licensure

- PCV13 is approved by the Food and Drug Administration for:
  - Children 6 weeks through 17 years of age
  - Adults 50 years of age and older
- ACIP recommended use of PCV13 for immunocompromised persons 6 years and older (2012, 2013)
- ACIP recommended use of PCV13 for all adults in 2014

# PCV13 IN CHILDREN

# ACIP Recommendations for PCV13

- Routine vaccination recommendation the same as for PCV7 (children 2-59 months)
  - 4 doses at 2, 4, 6, and 12 to 15 months
  - Fewer doses if series started at 7 months of age or older
- Children who have received 1 or more doses of PCV7 should complete the immunization series with PCV13

*MMWR* 2010;59(No. 9):258-61

# Pneumococcal Conjugate Vaccine Schedule for Unvaccinated Older Children-Primary Series

| Age at First Dose | # of Doses | Booster |
|---|---|---|
| 7-11 months | 2 doses | Yes |
| 12-23 months | 2 doses* | No |
| 24-59 months | 1 dose | No |
| 24-71 months, medical conditions** | 2 doses* | No |

*separated by at least 8 weeks; see MMWR 2010;59(RR-11):1–19

** chronic heart, lung disease, diabetes, CSF leak, cochlear implant, sickle-cell disease, other hemoglobinopathies, functional or anatomic asplenia, HIV infection, immunocompromising conditions

# ACIP Recommendations for PCV13 Supplemental Dose

- **A single supplemental dose of PCV13 is recommended for children who have received a complete age-appropriate series of PCV7:**
  - Healthy children 14 through 59 months
  - Children with an underlying medical condition 14 through 71 months (including those who have already received a dose of PPSV)

*MMWR* 2010;59(No. 9):258-61

# ACIP Recommendations for PCV13 Children

- Children aged 24–71 months with underlying medical conditions who received fewer than 3 doses of PCV7, should receive 2 doses of PCV13 (8 weeks apart)
- Children aged 24-71 months with underlying conditions who received any incomplete schedule of three doses of PCV7 before age 24 months should receive one dose of PCV13

# ACIP Recommendations for PCV13 Dose

- A dose of PCV13 should be administered to children 6 through 18 years of age who are at increased risk for invasive pneumococcal disease* ( and no prior PCV13 doses)
  - Functional or anatomic asplenia, including sickle cell disease
  - HIV infection and other immunocompromising conditions
  - Cochlear implant
  - CSF leak
- Regardless of previous history of PCV 7 or PPSV vaccine

*Off-label recommendation: ACIP vote, February 20, 2013

TABLE 1. Underlying medical conditions that are indications for pneumococcal vaccination among children, by risk group — Advisory Committee on Immunization Practices (ACIP), United States, 2010

| Risk group | Condition |
|---|---|
| Immunocompetent children | Chronic heart disease* |
| | Chronic lung disease† |
| | Diabetes mellitus |
| | Cerebrospinal fluid leaks |
| | Cochlear implant |
| Children with functional or anatomic asplenia | Sickle cell disease and other hemoglobinopathies |
| | Congenital or acquired asplenia, or splenic dysfunction |
| Children with immunocompromising conditions | HIV infection |
| | Chronic renal failure and nephrotic syndrome |
| | Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation |
| | Congenital immunodeficiency§ |

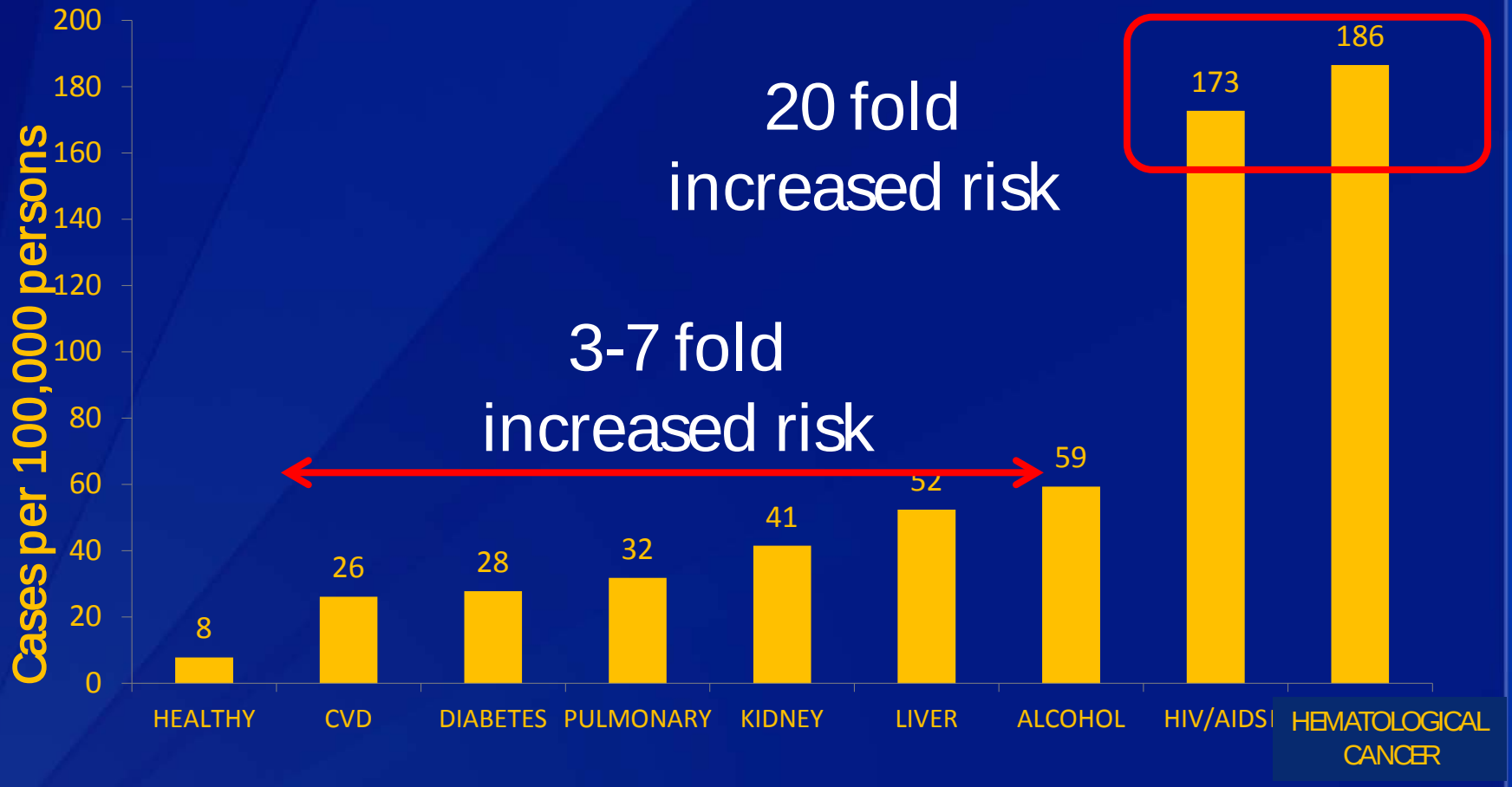
*Particularly cyanotic congenital heart disease and cardiac failure.
†Including asthma if treated with prolonged high-dose oral corticosteroids.
§Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

# PCV13 USE IN ADULTS

# PCV13 for Adults

- Licensed for use among adults >50 years old on 12/30/11
- FDA approved under the Accelerated Approval Pathway
- Based on non-inferior immunogenicity compared to PPSV23
- Post-approval condition of licensure:
  - Randomized controlled trial of PCV13 against pneumococcal pneumonia among adults ≥65 years old in the Netherlands

# Incidence of IPD in Adults Aged 18-64 Years with Selected Underlying Conditions, United States, 2009




Active Bacterial Core Surveillance, 2009. Unpublished data

# ACIP Recommendations June 2012
# PCV13 for Immunocompromised Adults - Rationale

- Extremely high burden of disease among immunocompromised adults
- Benefits outweigh any risks for use of PCV13 in some adults
- Indirect effects of PCV13 use in children not likely to eliminate IPD due to PCV13 serotypes in adults
- PCV13 use alone may not provide adequate coverage of serotypes causing disease in adults
- Combined use of PCV13 and PPSV23 more effective than either vaccine alone

# Morbidity and Mortality Weekly Report (*MMWR*)





## Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

*Weekly*
**October 12, 2012 / 61(40);816-819**

On June 20, 2012, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants (Table). PCV13 should be administered to eligible adults in addition to the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck & Co. Inc.), the vaccine currently recommended for these groups of adults (*1*). The evidence for the benefits and risk of PCV13 vaccination of adults with immunocompromising conditions was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and designated as a Category A recommendation (*2*,*3*). This report outlines the new ACIP recommendations for PCV13 use; explains the recommendations for the use of PCV13 and PPSV23 among adults with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants; and summarizes the evidence considered by ACIP to make its recommendations.

### Epidemiology of Pneumococcal Infection in Immunocompromised Adults

*Streptococcus pneumoniae* (pneumococcus) remains a leading cause of serious illness, including bacteremia, meningitis, and pneumonia among adults in the United States. An estimated 4,000 deaths occur in the United States each year because of *S. pneumoniae*, primarily among adults (*4*). The incidence of invasive disease ranges from 3.8 per 100,000 among persons aged 18–34 years to 36.4 per 100,000 among those aged ≥65 years (*4*). Adults with certain medical conditions also are at increased risk for invasive pneumococcal disease (IPD). For adults aged 18–64 years with hematologic cancer, the rate of IPD in 2010 was 186 per 100,000, and for persons with human immunodeficiency virus (HIV) the rate was 173 per 100,000 (CDC, unpublished data, 2012). The disease rates for adults in these groups can be more than 20 times those for adults without high-risk medical conditions.

PCV13 has been used for children since 2010, when it replaced an earlier version targeting seven serotypes (PCV7; Prevnar, Pfizer) that had been in use since 2000. The routine use of PCV7 in infants and young children resulted in significant reductions in IPD caused by vaccine serotypes in children, and because of indirect effects, also in adults. Rates of IPD caused by vaccine serotypes in adults aged 18–64 years without HIV decreased from six cases to

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm?s_cid=mm6140a4_w

| Risk Group | Underlying Medical Condition | PCV13 | PPSV23 | |
|---|---|---|---|---|
| | | Recommended | Recommended | Revaccination at 5 years |
| Immunocompetent persons | Chronic heart disease | | ✓ | |
| | Chronic lung disease | | ✓ | |
| | Diabetes mellitus | | ✓ | |
| | CSF leaks | ✓ | ✓ | |
| | Cochlear implants | ✓ | ✓ | |
| | Alcoholism | | ✓ | |
| | Chronic liver disease | | ✓ | |
| | Cigarette smoking | | ✓ | |
| Persons with functional or anatomic asplenia | Sickle cell disease/other hemaglobinopathies | ✓ | ✓ | ✓ |
| | Congenital or acquired asplenia | ✓ | ✓ | ✓ |
| Immunocompromised persons | Congenital or acquired immunodeficiencies | ✓ | ✓ | ✓ |
| | HIV infection | ✓ | ✓ | ✓ |
| | Chronic renal failure | ✓ | ✓ | ✓ |
| | Nephrotic syndrome | ✓ | ✓ | ✓ |
| | Leukemia | ✓ | ✓ | ✓ |
| | Lymphoma | ✓ | ✓ | ✓ |
| | Hodgkin disease | ✓ | ✓ | ✓ |
| | Generalized malignancy | ✓ | ✓ | ✓ |
| | Iatrogenic immunosuppression | ✓ | ✓ | ✓ |
| | Solid organ transplant | ✓ | ✓ | ✓ |
| | Multiple myeloma | ✓ | ✓ | ✓ |

# ACIP Recommendations for PCV13 for Immunocompromised Adults*

- **Adults 19 years of age or older with:**
  - Immunocompromising conditions
  - Functional or anatomic asplenia
  - CSF leaks
  - Cochlear implants

- Have not previously received PCV13 or PPSV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later, with a booster dose or PPSV23 5 or more years later

**MMWR* October 12, 2012 / 61(40);816-819

# PCV 13 in Adults - 2014

- ACIP now recommends PCV13 for adults 65 years old and older
- Some adults have received PCV13 already

# PPSV23 USE IN CHILDREN AND ADULTS

# Pneumococcal Polysaccharide Vaccine Recommendations

- **Persons 2 years and older with normal immune systems who have chronic illness**
  - Cardiovascular or pulmonary disease (asthma if ≥19 years)
  - Diabetes
  - Liver disease
  - Alcoholism
  - Smoking (≥19 years)
  - CSF leak
  - Cochlear implant
- **Persons in environments or settings with increased risk**

# Pneumococcal Polysaccharide Vaccine Recommendations

- **Persons 2 years and older who are immunocompromised (due to disease or treatment)**
  - Asplenia (functional or anatomic)
  - Chronic renal failure
  - Nephrotic syndrome
  - Hodgkin disease
  - Lymphoma and leukemia
  - Multiple myeloma
  - Organ transplant
  - HIV infection

# Pneumococcal Polysaccharide Vaccine Revaccination

- Routine revaccination of immunocompetent persons is not recommended
- Revaccination recommended for persons 2-64 years of age who are at highest risk of serious pneumococcal infection

*MMWR* 2010;59(No.34):1102-5

# Pneumococcal Polysaccharide Vaccine Candidates for Revaccination

- **Five year interval (2-64 Years) with additional dose after 65th birthday, five years after previous dose:**
  - Functional or anatomic asplenia (including sickle cell disease)
  - Immunosuppression (including HIV infection)
  - Transplant
  - Chronic renal failure
  - Nephrotic syndrome

- **Only one dose recommended after 65th birthday**

*MMWR* 2010;59(No.34):1102-5 and 2010;59(RR-11)

# Pneumococcal Polysaccharide Vaccine Candidates for Revaccination

- **One dose between 2-64 years, with repeat dose after 65th birthday and five year interval from previous dose**
  - Chronic heart disease
  - Chronic lung disease (asthma in persons 19-64 years)
  - Diabetes mellitus
  - Chronic liver disease
  - CSF leak
  - Cochlear implant
  - Alcoholism
  - Cigarette smoking in persons 19-64 years
- **Only one dose recommended after 65th birthday**

# Administering PCV13 and PPSV23 Vaccines General Rules

- PCV13 and PPSV23 should not be administered during the same clinic visit
  - Either vaccine may be administered simultaneously with influenza vaccine
- Administer PCV13 before PPSV23 whenever possible

# ACIP Recommendations for PPSV23 for Adults 19 Years and Older 2010

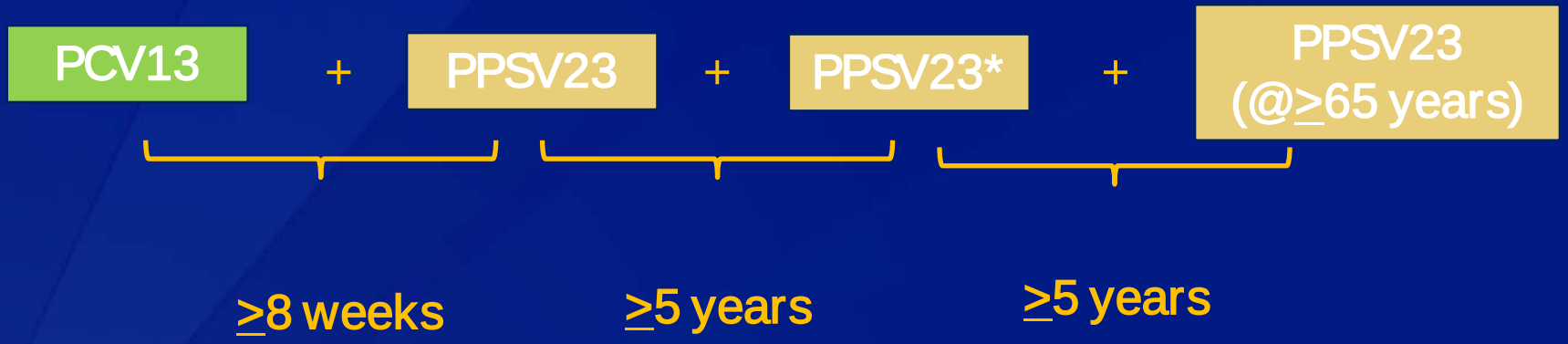
- Immunocompetent w/ underlying condition


- Asplenic (sickle cell, hemoglobinopathy), Immunocompromised


- 65 years or older

# ACIP Recommendations for PCV13 and PPSV23 for Adults 19 Years and Older 2012

- Immunocompromised, Asplenic (sickle cell, hemoglobinopathy), CSF leaks, Cochlear Implants who are Pneumococcal-naive

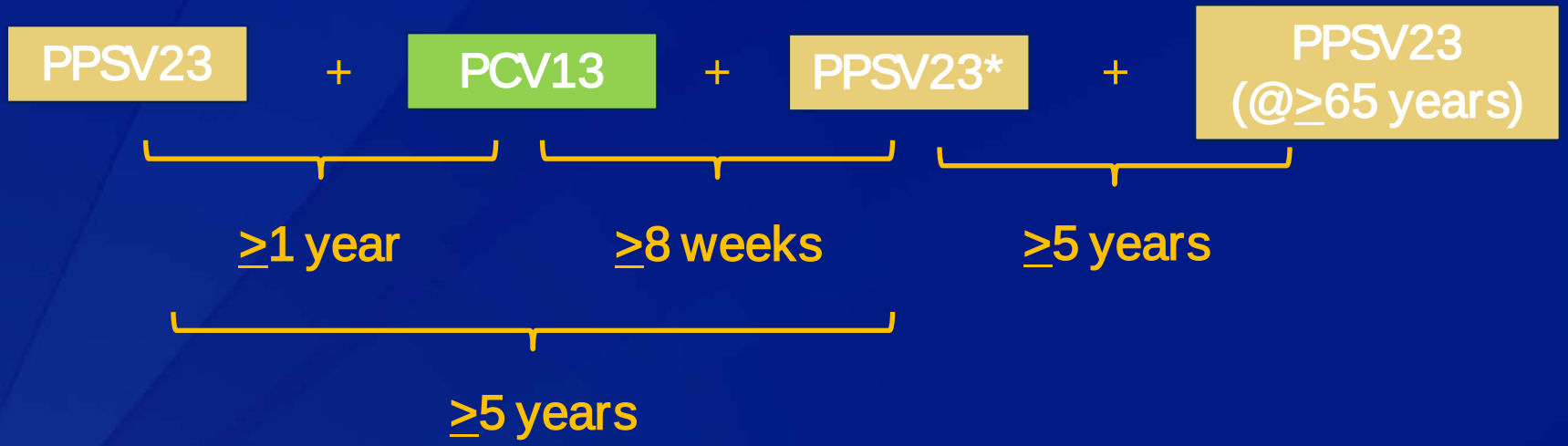



*Second PPSV23 dose before age 65 years NOT recommended for adults with CSF leaks or those with cochlear implants

*ACIP off-label recommendation for PCV13 for adults 19 through 49 years of age

# ACIP Recommendations for PCV13 and PPSV23 for Adults 19 Years and Older 2012

- Immunocompromised, Asplenic (sickle cell, hemoglobinopathy), CSF leaks, Cochlear Implants who have previously received PPSV23

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# ACIP Recommendations for PCV13 and PPSV23 for Adults 65 Years and Older 2014ears

- Pneumococcal-naïve or Unknown vaccination history
- Healthy adult


- If PPSV23 cannot be given at 12 months later, it should be given during the next visit
- Minimum interval = 8 weeks

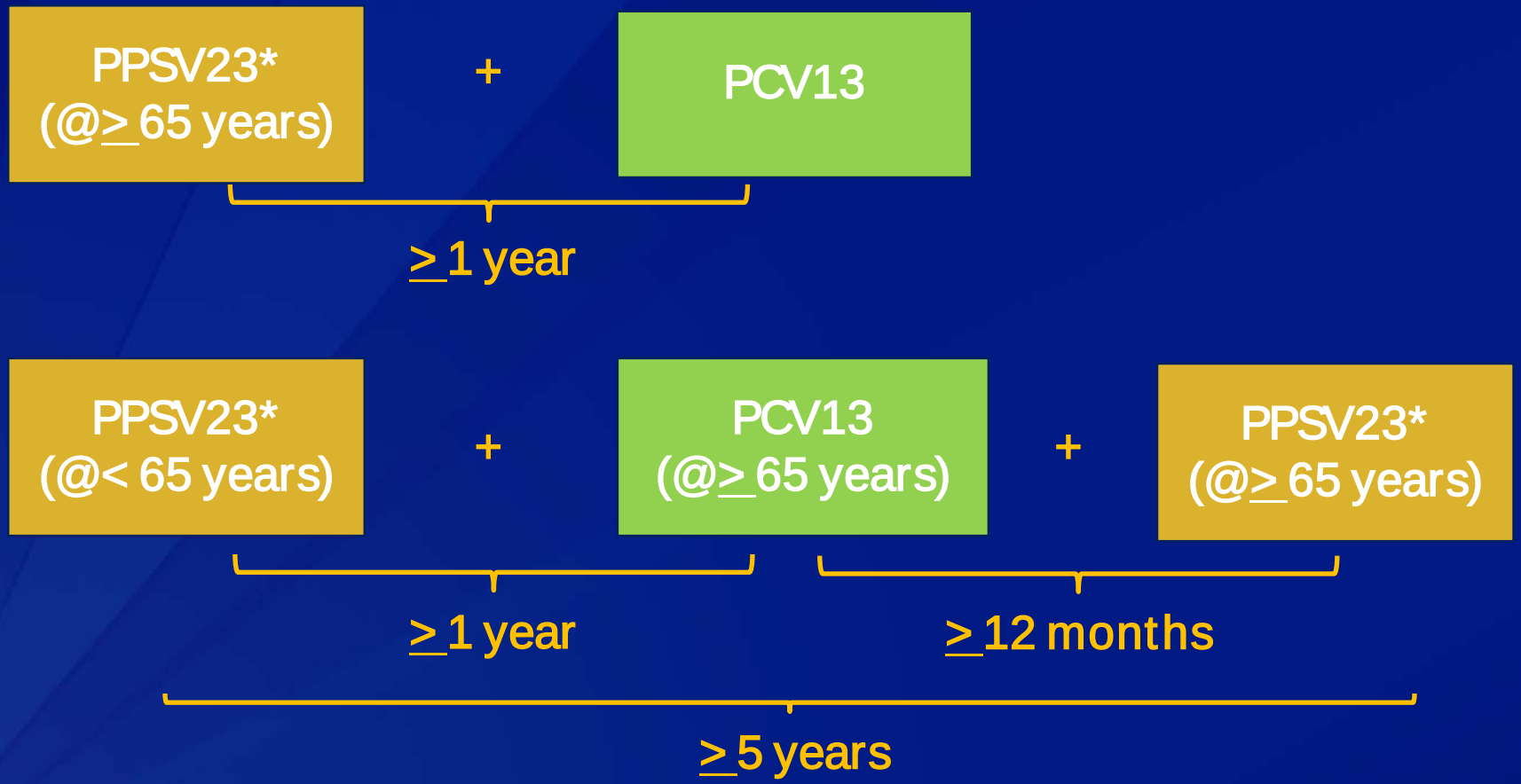
# ACIP Recommendations for PCV13 and PPSV23 for Adults 65 Years and Older 2014ears

- Pneumococcal-naïve or Unknown vaccination history
- High-risk adult


- Minimum interval = 8 weeks

# ACIP Recommendations for PCV13 and PPSV23 for Adults 65 Years and Older 2014

- Previously received one or more doses of PPSV23
- Healthy adult




*Doses already administered

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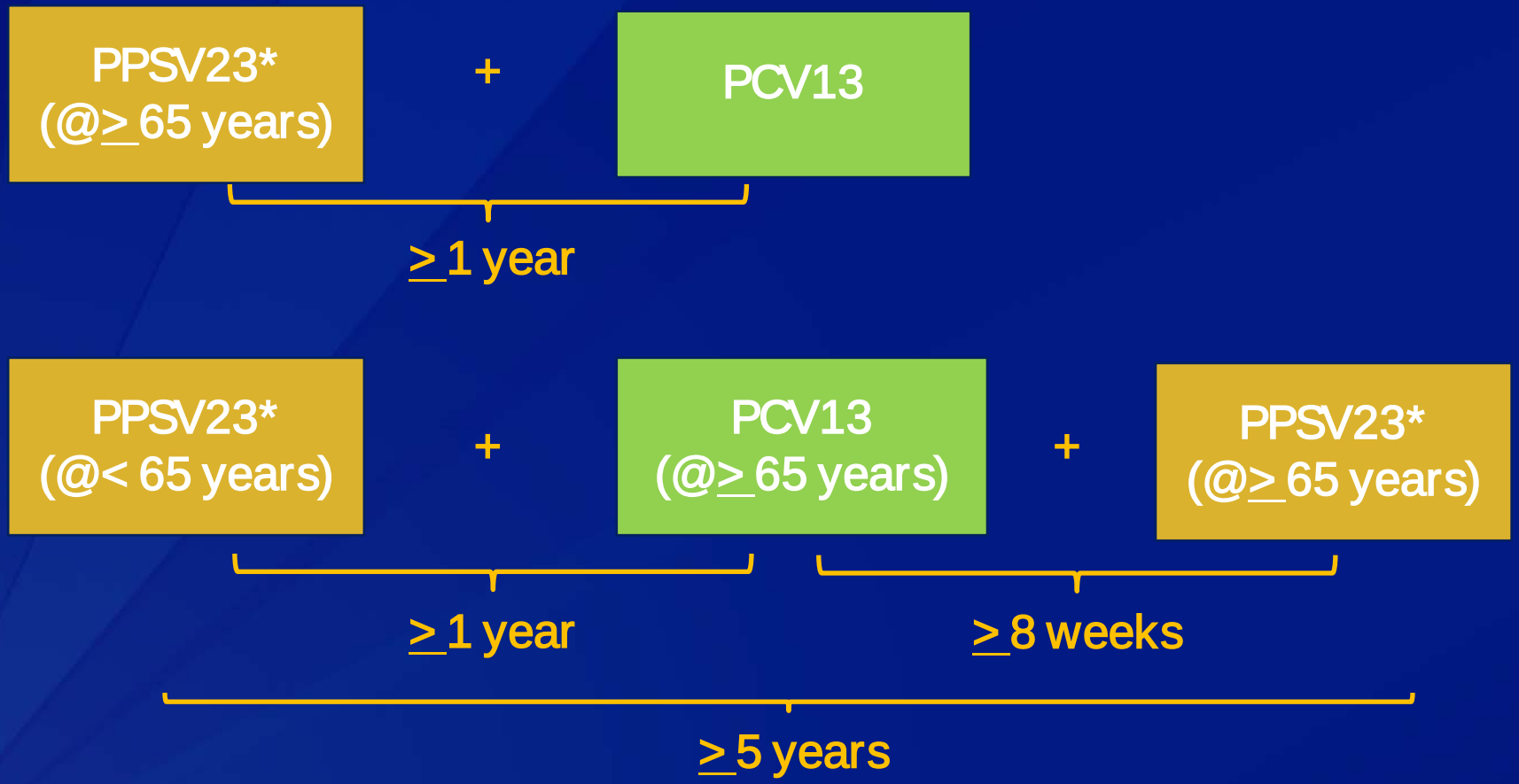
- Previously received one or more doses of PPSV23
- High-risk adult




*Doses already administered

# Pneumococcal Vaccines Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose of vaccine
- Moderate or severe acute illness

# Pneumococcal Vaccines Adverse Reactions

| | PPSV23 | PCV |
|---|---|---|
| Local reactions | 30%-50% | 5%-49% |
| Fever, myalgia | <1% | 24-35% |
| Febrile seizures | --- | Rare: 1-14/100,000; with IIV 4 - 45/100,000 |
| Severe adverse reactions | rare | 8% (local) |

# Febrile Seizures: Simultaneous Vaccination

- Vaccine Safety Datalink looked at 200,000 children 6 months through 4 years of age vaccinated 2010-11
- Rate of febrile seizures with simultaneous PCV13 and IIV vaccination was 2.5 times higher than PCV13 alone, and 2.4 times higher than IIV alone.
- Febrile seizures are benign and risk of disease high for infants (for both influenza and invasive pneumococcal disease)
- No change in recommendations, vaccines should be given simultaneously if both are indicated.

# Pneumococcal* Vaccine Coverage, 2012

- Healthy People 2020 goal: 90% coverage for persons 65 years of age or older
- 2005 Behavioral Risk Factor Surveillance System 64% of persons 65 years of age or older ever vaccinated
- Vaccination coverage levels much lower (20%) among persons 18-64 years of age with a chronic illness

*Type of pneumococcal vaccine received unknown;
MMWR February 7, 2014 / 63(05);95-102

# Pneumococcal Polysaccharide Vaccine Missed Opportunities

- >65% of patients with severe pneumococcal disease had been hospitalized within preceding 3–5 years yet few had received vaccine

# Pneumococcal Resources

- ACIP's Pneumococcal Recommendations web page
  www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html
- CDC's Pneumococcal Infection web page
  www.cdc.gov/pneumococcal/index.html
- CDC's Pneumococcal Vaccination web page
  PCV - www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm
  PPSV - www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm
- Immunization Action Coalition Pneumococcal web page
  PCV - www.immunize.org/pneumococcal-pcv/
  PPSV – www.immunize.org/pneumococcal-ppsv/
- Children's Hospital of Philadelphia Vaccine Education Center Pneumococcal web page
  www.chop.edu/service/vaccine-education-center/a-look-at-each-vaccine/pneumococcus-vaccine.html