Pneumococcal Vaccines

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Number: 0037

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses pneumococcal vaccines.

1. **Medical Necessity**

   Aetna considers U.S. Food and Drug Administration (FDA)-approved pneumococcal conjugate vaccines (PCV15, PCV20, PCV21) and pneumococcal polysaccharide vaccine (PPSV23) medically necessary according to the recommendations of the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP). Pneumococcal vaccines are considered medically necessary (unless otherwise specified) for the following groups:

   1. **Infants, children, adolescence**

      1. Pneumococcal 15-valent conjugate vaccine (PCV15; Vaxneuvance) or pneumococcal 20-valent conjugate vaccine (PCV20; Prevnar 20) for all children aged 2 through 59 months (less than 5 years of age) according to currently recommended PCV dosing and schedules. **Note:** Children who started with PCV13 (Prevnar 13) can finish the series with PCV15 or PCV20;
      2. Children with an incomplete pneumococcal vaccination status, use of either PCV15 or PCV20 according to current PCV dosing and schedule as catch-up vaccination for:

         1. Healthy children aged 24 through 59 months (2 years to less than 5 years of age); *or*
         2. Children aged 24 through 71 months (2 years to less than 6 years of age) who have underlying health conditions** that increase risk for pneumococcal disease;

      3. Children aged 2 through 18 years with any risk condition who have received all recommended doses of PCV before age 6 years; *and*

         1. Received at least one dose of PCV20, additional doses of any pneumococcal vaccine are considered not medically necessary; *or*
         2. Received PCV13 or PCV15 and did not receive a PCV20 vaccine, a dose of PCV20 or 23-valent pneumococcal polysaccharide vaccine (PPSV23, e.g., Pneumovax 23) is considered considered medically necessary;

      4. Children aged 6 through 18 years with any risk condition who have not received any dose of PCV13, PCV15, or PCV20, a single dose of PCV15 or PCV20 is considered medically necessary. **Note:** When PCV15 is used, a follow-up dose of PPSV23 (Pneumovax 23) is recommended by the ACIP to be administered at least 8 weeks later if not previously given;

   2. **Adults 19 through 49 years**

      PCV15 (Vaxneuvance), PCV20 (Prevnar 20), or PCV21 (Capvaxive) for adults 19 through 49 years of age who have underlying health conditions * that increase risk for pneumococcal disease and have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown.

Notes:

1. If PCV15 is used, a single dose of PPSV23 may be administered 1 year or more after the PCV15 dose. Administration after 8 weeks or more can be considered in adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak (CSF).
2. If PCV20 or PSV21 is used, it does not need to be followed by PPSV23. Regardless of vaccine used (PPCV20 or PPSV23), the member's pneumococcal vaccinations are complete.
3. If previously received PPSV23 only, a single dose of PCV21, PCV20, or PCV15 may be administered at least 1 year after the last PPSV23 dose.
4. If previously received PCV13 only, a single dose of PCV21 or PCV20 may be administered at least 1 year after the PCV13 dose.

(Kobayashi et al, 2025)

3. **Adults 50 years of age or older**

    1. PCV15 (Vaxneuvance), PCV20 (Prevnar 20), or PCV21 (Capvaxive) for all adults 50 years of age or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown.

        Notes:

        1. If PCV15 is used, this should be followed by a dose of PPSV23 (Pneumovax 23) at least 1 year later. A minimum interval of 8 weeks can be considered if PCV15 is used in adults with an immunocompromising condition, cochlear implant, or CSF leak.
        2. If PCV20 or PCV21 is used, a dose of PPSV23 is not indicated. Regardless of which vaccine is used (PCV20 or PCV21), the member's pneumococcal vaccinations are complete.
        3. If previously received PPSV23 only, a single dose of PCV21, PCV20, or PCV15 may be administered at least 1 year after the last PPSV23 dose.
        4. If previously received PCV13 only, a single dose of PCV21 or PCV20 may be administered at least 1 year after the PCV13 dose.

        (Kobayashi et al, 2025)

    2. Based on shared clinical decision-making, adults 65 years or older have the option to get PCV20 or PCV21, or to not get additional pneumococcal vaccines. Members can get PCV20 or PCV21 if they have received both:

        1. PCV13 (but not PCV15, PCV20, or PCV21) at any age; and
        2. PPSV23 at or after the age of 65 years old.

* Risk conditions include:

1. alcoholism
2. cerebrospinal fluid leak
3. chronic heart disease, including congestive heart failure and cardiomyopathies
4. chronic liver disease
5. chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma
6. chronic renal failure or nephrotic syndrome
7. cigarette smoking
8. cochlear implant
9. congenital or acquired asplenia
10. congenital or acquired immunodeficiency (i.e., B- [humoral] or T-lymphocyte deficiency, complement deficiency, phagocytic disorder [excluding chronic granulomatous disease])
11. diabetes mellitus
12. generalized malignancy
13. HIV infection
14. Hodgkin disease
15. iatrogenic immunosuppression, including long-term systemic corticosteroids and radiation therapy
16. leukemia
17. lymphoma
18. multiple myeloma
19. sickle cell disease or other hemoglobinopathies
20. solid organ transplant (CDC, 2023b).

** Risk conditions include:

1. cerebrospinal fluid leak
2. chronic heart disease
3. chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions)
4. chronic liver disease
5. chronic lung disease (including moderate persistent or severe persistent asthma)
6. cochlear implant
7. diabetes mellitus
8. immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome)
9. congenital or acquired asplenia or splenic dysfunction
10. congenital or acquired immunodeficiencies
11. diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant
12. HIV infection; and
13. sickle cell disease and other hemoglobinopathies) (CDC, 2023a).

Aetna considers quantitation of Streptococcus pneumoniae antibody (IgG) to assess impaired antibody response to pneumococcal polysaccharide vaccine medically necessary to diagnose immunodeficiency syndromes in persons with recurrent bacterial infections, and to assess their eligibility for parenteral immunoglobulin replacement (see CPB 0206 - Parenteral Immunoglobulins).

2. **Experimental, Investigational, or Unproven**

Aetna considers pneumococcal conjugate vaccines (PCV13, PCV15, PCV20, and PCV21) and pneumococcal polysaccharide vaccine (PPSV23) experimental, investigational, or unproven for other groups because its effectiveness for groups other than the ones listed in Section I (above) has not been established.

Aetna considers quantitation of Streptococcus pneumoniae antibody experimental, investigational, and unproven for diagnosing pneumococcal infections and for all other indications because its clinical value for these indications has not been established.

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
90671	Pneumococcal conjugate vaccine, 15 valent (PCV15), for intramuscular use
90677	Pneumococcal conjugate vaccine, 20 valent (PCV20), for intramuscular use
90684	Pneumococcal conjugate vaccine, 21 valent (PCV21), for intramuscular use
90732	Pneumococcal polysaccharide vaccine, 23-valent, adult or immunosuppressed patient dosage, when administered to individuals 2 years or older, for subcutaneous or intramuscular use

CPT codes not covered for indications listed in the CPB:

87652	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, quantification

Other CPT codes related to the CPB:

90460	Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional; first or only component of each vaccine or toxoid administered
+90461	each additional vaccine or toxoid component administered (List separately in addition to code for primary procedure)
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); 1 vaccine (single or combination vaccine/toxoid)
+90472	each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure)

HCPCS codes covered if selection criteria are met:

G0009	Administration of pneumococcal vaccine

Code	Code Description
Other HCPCS codes related to the CPB:	
G0310	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0311	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 16-30 mins time (this code is used for Medicaid billing purposes)
G0312	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0313	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 16-30 mins time (this code is used for Medicaid billing purposes)
ICD-10 codes covered if selection criteria are met:	
Z23	Encounter for immunization [pneumococcus]
Streptococcus pneumoniae antibody (IgG):	
CPT codes covered if selection criteria are met:	
86581	Streptococcus pneumoniae antibody (IgG), serotypes, multiplex immunoassay, quantitative
ICD-10 codes covered if selection criteria are met:	
A30 - A49	Other bacterial diseases

Background

This policy is based on the recommendations of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (CDC/ACIP), the U.S. Preventive Services Task Force (USPSTF), the American Academy of Pediatrics (AAP) Committee on Infectious Diseases, the American College of Physicians Task Force on Adult Immunization, and the Infectious Diseases Society of America.

Pneumococcal disease is an infection with the bacteria *Streptococcus pneumoniae*, which causes pneumonia, bacteremia, and meningitis. Pneumococcal disease is a significant cause of morbidity and mortality in the United States. Population-based surveillance studies have reported annual invasive pneumococcal disease rates of at least 15 to 19/100,000 population and pneumococcal meningitis rates of 0.3 to 1.2/100,000. Significantly higher incidence rates are reported for persons less than 5 years of age or over age 65; African Americans, Native Americans, and Alaska Natives; nursing home residents; alcoholics; and those with chronic medical or immunodeficient conditions.

Pneumococcal disease accounts for about 15 % of severe community-acquired pneumonia, which has a case-fatality rate (proportion of cases resulting in death) of 9 to 26 %. Pneumococcal bacteremia and meningitis are also associated with high case-fatality rates. The highest case-fatality rates from invasive pneumococcal infection occur in elderly persons (30 to 43 %) and patients with co-morbid conditions (25 to 27 %).

Advisory Committee on Immunization Practices (ACIP) Recommendations

There are 2 types of pneumococcal vaccines available in the United States: Pneumococcal conjugate vaccines (PCV13, PCV15, PCV20, and PVC21) and pneumococcal polysaccharide vaccine (PPSV23).

On October 20, 2021, the ACIP recommended 15-valent PCV (PCV15) or 20-valent PCV (PCV20) for PCV–naïve adults who are either aged 65 years or older or aged 19 through 64 years with certain underlying conditions. When PCV15 is used, it should be followed by a dose of PPSV23, typically 1 year or more later.

On June 22, 2022, ACIP updated the recommendations for use of the PCV15 among U.S. children as an option for pneumococcal conjugate vaccination for persons less than 19 years of age, according to currently recommended PCV13 dosing and schedules. Risk-based recommendations on use of PPSV23 were not changed. ACIP recommends use of PCV (either

PCV13 or PCV15) for all children aged 2 months through 59 months. In addition, risk-based PCV use is recommended for children aged 60 through 71 months with risk conditions, and persons aged 6 years through 18 years with an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant. For all recommendations, PCV13 and PCV15 can be used interchangeably. Interruption of the vaccination schedule does not require reinstitution of the entire series or the addition of extra doses (Kobayashi et al, 2022b).

On June 22, 2023, the Pneumococcal Vaccines Work Group for ACIP met to review the evidence on recommendations for use of PCV20 in children. They voted to add the 20-valent vaccine as an option for pediatrics and expanded its definition of high-risk children to include those with moderate persistent and severe persistent asthma. These recommendations were adopted by the CDC Director on June 27, 2023 and are now official. They will be published in MMWR in the coming months (CDC, 2023):

- Use of either pneumococcal conjugate vaccines (PCV) PCV15 or PCV20 is recommended for all children aged 2–23 months according to currently recommended PCV dosing and schedules.
- For children with an incomplete PCV vaccination status, use of either PCV15 or PCV20 according to currently recommended PCV dosing and schedules is recommended for:
    - Healthy children aged 24–59 months
    - Children with specified health conditions*** aged 24 through 71 months
- For children aged 2–18 years with any risk condition who have received all recommended doses of PCV before age 6 years
    - Using ≥1 dose(s) of PCV20: No additional doses of any pneumococcal vaccine are indicated. This recommendation may be updated as additional data become available.
    - Using PCV13 or PCV15 (no PCV20): A dose of PCV20 or PPSV23 using previously recommended dosing and schedules is recommended.
- For children aged 6–18 years with any risk condition who have not received any dose of PCV13, PCV15, or PCV20, a single dose of PCV15 or PCV20 is recommended. When PCV15 is used, it should be followed by a dose of PPSV23 at least 8 weeks later if not previously given.

*** Risk conditions include: cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; diabetes mellitus; immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease and other hemoglobinopathies) (CDC, 2023).

Although still available in the United States, the Centers for Disease Control and Prevention (CDC) no longer recommends the 13-valent pneumococcal conjugate vaccine (PCV13) for children or adults. In 2024, the Advisory Committee on Immunization Practices (ACIP) removed the recommendation for routine PCV13 use in children and adolescents in the United States. PCV20 is the current preferred pneumococcal conjugate vaccine, offering broader protection than PCV13.

On June 27, 2024, the CDC's ACIP voted unanimously to recommend pneumococcal 21-valent conjugate vaccine (PCV21), Capvaxive (Merck & Co., Inc) as an option for adults 65 years of age and older for the prevention of invasive pneumococcal disease and pneumococcal pneumonia. Specifically, the ACIP voted to recommend a single intramuscular dose of PCV21 for the following indications:

- Adults 65 years of age and older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown;
- Adults 19-64 years of age with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown;
- Adults 19 years of age and older who have started their pneumococcal vaccine series with PCV13 (pneumococcal 13-valent conjugate vaccine) but have not received all recommended PPSV23 (pneumococcal 23-valent polysaccharide vaccine) doses.

Moreover, ACIP recommended shared clinical decision-making regarding use of a supplemental dose of PCV21 for adults 65 years of age and older who have completed their vaccine series with both PCV13 and PPSV23.

PCV21 includes eight new pneumococcal serotypes that are not contained in currently available pneumococcal vaccines. PCV21 does not include certain serotypes that used to be common before the introduction of PCV but are now infrequent among the general adult population. Because of the differences, some healthcare providers might recommend a supplemental dose of PCV21 for people who completed their pneumococcal vaccine series with another pneumococcal vaccine. Therefore, the ACIP

recommends adults 65 and older who completed their series with an earlier vaccine to talk with their healthcare provider about PCV21.

In regards to the different pneumococcal vaccine options, the chair of the Indian Health Service National Pharmacy & Therapeutics Committee stated that choices were important for certain populations because they contain so many different serotypes. For example, the PCV21 does not contain some serotypes that are in current vaccines, such as serotype 4 which has "emerged as a substantial contribution to invasive pneumococcal disease in adults and adults in Alaska and in the Navajo Nation, but that is only covered by PCV20" (Rosenthal, 2024).

The updated ACIP recommendations were adopted by the CDC Director and became official June 27, 2024.

In October 2024, the CDC's ACIP extended their recommendations to include routine pneumococcal vaccinations for: (i) a 4-dose PCV series (PCV15 or PCV20) for all children younger than 5 years old; and (ii) PCV15, PCV20, or PCV21 for all adults 50 years of age or older. Moreover, recommendations included shared clinical decision-making for adults 65 years or older who have the option to get PCV20 or PCV21, or to not get additional pneumococcal vaccines. They can get PCV20 or PCV21 if they have received both PCV13 (but not PCV15, PCV20, or PCV21) at any age and PPSV23 at or after the age of 65 years old (CDC, 2024b, 2024c, 2024d; Kobayashi et al, 2025).

Children who started with an PCV13 can finish with PCV15 or PCV20 (CDC, 2024c).

Among adults aged 19 years or older who have started their pneumococcal vaccination series with PCV13 but have not received all recommended doses, PPSV23 is no longer recommended as an option to complete the series. Either PCV20 or PCV21 is recommended to complete the series (Kobayashi et al, 2025).

ACIP Recommendations for Shared Clinical Decision-Making

Advisory Committee on Immunization Practices (ACIP) generally makes shared clinical decision-making recommendations when individuals may benefit from vaccination, but broad vaccination of people in that group is unlikely to have population-level impacts. Shared clinical decision-making recommendations are individually based and informed by a decision process between the health care provider and the patient or parent/guardian. The CDC defines a health care provider as anyone who provides or administers vaccines: primary care physicians, specialists, physician assistants, nurse practitioners, registered nurses, and pharmacists (CDC, 2023c).

Health care providers can find information on ACIP’s recommendations on the ACIP Vaccine Recommendations and Guidelines page.

For every ACIP recommendation, CDC publishes a policy note in the Morbidity and Mortality Weekly Report (MMWR), which provides background and considerations on each recommendation.

Pneumococcal Polysaccharide Vaccine (PPSV23)

Pneumococcal polyvalent vaccine is available as Pneumovax 23 (Merck & Co., Inc) and is supplied as a 0.5 mL single-dose vial and a single-dose prefilled syringe for intramuscular or subcutaneous injection. Pneumovax 23 is FDA approved for use in persons 50 years of age or older and persons aged 2 years and older who are at increased risk for pneumococcal disease. Pneumovax 23 is not approved for use in children younger than 2 years of age because children in this age group do not develop an effective immune response to capsular types contained in the polysaccharide vaccine. Response to vaccination may be diminished in immunocompromised individuals.

Pneumovax 23 is a vaccine indicated for active immunization for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F).

Pneumococcal polysaccharide vaccine (Pneumovax 23) contains 23 purified capsular polysaccharide antigens of *S. pneumoniae*, and is protective against 88 % of the strains of S. pneumoniae causing bacteremic pneumococcal disease reported in the United States. The 6 serotypes that most frequently cause invasive drug-resistant pneumococcal infection in the United States are represented in the 23-valent vaccine. These vaccines were licensed in the United States in 1983 and replaced an earlier 14-valent formulation that was licensed in 1977.

Clinical studies have demonstrated the effectiveness of standard pneumococcal vaccine in reducing the incidence of pneumococcal pneumonia in the elderly and in immunocompetent high-risk groups. A meta-analysis combining the most recent trials reported that vaccinated individuals had 11 fewer episodes of definitive pneumococcal pneumonia and 25 fewer episodes of presumptive pneumococcal pneumonia per 1,000 subjects (Fine, 1994). Case-control studies and indirect cohort studies support the protective value of vaccine in immunocompetent recipients, with vaccine efficacy estimates of 60 to 75 % reported, but not in severely or relatively immunocompromised individuals, including those with alcoholism, chronic renal failure, immunoglobulin deficiency, nephrotic syndrome, sickle cell disease, multiple myeloma, metastatic or hematologic malignancies,

or systemic lupus erythematosus. For some of these disorders, efficacy point estimates suggest a benefit but the confidence intervals (CIs) are wide and include the possibility of no benefit.

The U.S. Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against pneumococcal vaccine as an efficacious vaccine for immunocompromised individuals, but noted that recommendations for vaccinating these persons may be made on other grounds, including high incidence and case-fatality rates of pneumococcal disease and minimal adverse effects from vaccine.

Immunocompromised conditions associated with high risk for pneumococcal disease include alcoholism, cirrhosis, chronic renal failure, nephrotic syndrome, sickle cell disease, multiple myeloma, metastatic or hematologic malignancies, acquired or congenital immunodeficiencies (including HIV infection), and other conditions associated with immunosuppression, such as organ transplant.

For most individuals, accepted guidelines suggest a single vaccination is sufficient. The CDC and UPSPTF do not recommend routine revaccination, but state that it may be appropriate to consider revaccination in certain immunocompetent individuals at highest risk for morbidity and mortality from pneumococcal disease who were vaccinated more than 5 years previously. These authorities also state that it may be appropriate to consider periodic re-vaccination of certain high-risk immunocompromised patients, who are likely to have poor initial antibody response and rapid decline of antibodies after vaccination. In addition, re-vaccination with the 23-valent pneumococcal polysaccharide vaccine may be appropriate for high-risk individuals who received the 14-valent polysaccharide vaccine, which was in use prior to 1983.

Pneumococcal vaccine may be given with other vaccines. No data indicate that administration of pneumococcal vaccine with DTP, poliovirus, or influenza increases the severity of reactions or diminishes the responses. However, in a randomized clinical study, a reduced immune response to Zostavax as measured by gpELISA was observed in individuals who received concurrent administration of Pneumovax 23 and Zostavax compared with individuals who received these vaccines 4 weeks apart. Thus, it is recommended that administration of the two vaccines be separated by at least 4 weeks (Merck, 2021b).

Pneumococcal vaccine is not indicated in the prophylaxis of otitis media in children. The safety of pneumococcal vaccine in pregnancy has not been evaluated.

There is insufficient evidence that pneumococcal vaccine effects the course of bronchiectasis. In a Cochrane review, Chang and colleagues (2007) assessed the effectiveness of pneumococcal vaccine as routine management in children and adults with bronchiectasis in reducing the severity and frequency of respiratory exacerbations and pulmonary decline. The authors concluded that currently there is a lack of reliable evidence to support or refute the routine use of pneumococcal vaccine as routine management in children and adults with bronchiectasis. Randomized controlled studies examining the effectiveness of this intervention using various vaccine types in different age groups are needed.

For subjects aged 65 years or older in a clinical study systemic adverse reactions, determined by the investigator to be vaccine-related, were higher following revaccination (33.1%) than following initial vaccination (21.7%). Routine revaccination of immunocompetent persons previously vaccinated with a 23-valent vaccine, is not recommended.

The most common adverse reactions, reported in more than 10% of subjects vaccinated with Pneumovax 23 for the first time in a clinical trial, were: injection-site pain/soreness/tenderness (60.0%), injection-site swelling/induration (20.3%), headache (17.6%), injection-site erythema (16.4%), asthenia and fatigue (13.2%), and myalgia (11.9%) (Merck, 2021b).

Heptavalent Pneumococcal Conjugate Vaccine (PCV7)

A 7-valent pneumococcal conjugate vaccine (Prevnar™, Prevenar™) was introduced by Wyeth Lederle for use in children. The FDA had approved of this protein-polysaccharide conjugate vaccine for prevention of invasive pneumococcal disease (meningitis and bacteremia) in infants and toddlers.

The American Academy of Pediatrics and the CDC's ACIP had recommended pneumococcal polyvalent vaccine for routine use in all children 2 and under, and for black, Alaskan Native, and Native American toddlers up to age 5, as well as for those with sickle-cell anemia, HIV infection, or other immunodeficiency diseases. For infants, the AAP and ACIP had recommended that the vaccine be given in 4 doses at 2, 4, 6, and 12 to 15 months; for children who are 7 to 11 months, 3 doses; for children who are 12 to 23 months, 2 doses; and for children 2 years or older, only 1 dose is needed.

Pneumococcus is the most frequent cause of otitis media, pneumonia, and bacteremia in children, as well as the principle cause of childhood bacterial meningitis. The most susceptible to pneumococcal diseases are children less than 2 years old. Standard pneumococcal polysaccharide vaccines are poorly immunogenic in this age group. The new protein-polysaccharide conjugate vaccine is immunogenic during infancy and is capable of providing long-term immunity.

Pneumococcal conjugate vaccine targets the seven serotypes (strains) of *Streptococcus pneumonia* that are responsible for 85 % of bacterial pneumonia in children. The serotypes contained in the vaccine are also commonly associated with antibiotic resistance.

There is reliable evidence of the effectiveness of pneumococcal conjugate vaccine. A 3-year, multi-center clinical trial involving 37,868 children reported that the pneumococcal conjugate vaccine was effective against invasive pneumococcal disease caused by seven prevalent serotypes of bacteria. Pneumococcal conjugate vaccine had an efficacy rate of 97 % against invasive pneumococcal disease with vaccine serotypes, and a 93 % efficacy rate for disease with any serotype. Children who received the pneumococcal vaccine were 1/3 less likely to develop x-ray confirmed pneumonia compared to children who received a conjugate meningococcal vaccine as a control. Children who received the vaccine were 73 % less likely to have had severe pneumonia, and 89 % less likely to develop pneumococcal meningitis and bacteremia. The results also suggested efficacy against frequent, recurrent otitis media; vaccinated children were 20% less likely to have otitis media severe enough to require drainage tubes.

In 2010, 7-valent pneumococcal conjugate vaccine (PCV7) was replaced with pneumococcal 13-valent conjugate vaccine (PCV13) (CDC, 2019).

Pneumococcal 13-valent Conjugate Vaccine (PCV13, Prevnar 13)

U.S. Food and Drug Administration (FDA)-Approved Indications

- In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is indicated for:
    - active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
    - active immunization for the prevention of otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A.

- In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:
    - active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
- In adults 18 years of age and older, Prevnar 13 is indicated for:
    - active immunization for the prevention of pneumonia and invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- Limitations of Prevnar 13 Use and Effectiveness
    - Prevnar 13 does not protect against disease caused by S. pneumoniae serotypes that are not in the vaccine.

Pneumococcal 13-valent conjugate vaccine is available as Prevnar 13 (Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc) and is supplied in a single-dose prefilled syringe as 0.5 mL suspension for intramuscular injection.

The CDC's ACIP voted on February 24, 2010 to recommend the use of a 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar 13) (Wyeth Pharmaceuticals Inc.), which provides broader protection for young children against pneumococcal diseases. The vote came after the FDA had approved the vaccine for active immunization of infants and children aged 6 weeks through 5 years (prior to the sixth birthday) against *Streptococcus pneumonia*, which causes invasive pneumococcal diseases, such as pneumonia and meningitis, and against otitis media. The new version of the vaccine protects against 6 more serotypes of *Streptococcus pneumonia* than the original version and is intended to replace PCV7. Unlike PCV7, PCV13 includes serotype 19A, which is the most common serotype causing invasive pneumococcal infections in children. In addition to serotype 19A, PCV13 also contains conjugated antigens representing serotypes 1, 3, 4, 5, 6A and B, 7F, 9V, 14, 18C, 19F, and 23F.

The FDA approval on February 24, 2010 was based on data from a clinical trial program including 13 core Phase 3 studies involving more than 7,000 infants and young children that showed the new 13-valent vaccine elicited immune responses comparable to that achieved with the 7-valent PCV. FDA 2010 product information identified a 4-dose infant/toddler schedule to be administered at ages 2 months, 4 months, 6 months, and 12 to 15 months.

Adverse events were similar for both vaccines and most commonly included injection site reactions (pain, erythema, and inflammation), as well as irritability, decreased appetite, and fever.

Labeled warnings and precautions include apnea following intramuscular vaccination which has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

Adverse reactions, per the label, include the following:

- In infants and toddlers vaccinated at 2, 4, 6, and 12–15 months of age in US clinical trials, the most commonly reported solicited adverse reactions (greater than 5%) were irritability (greater than 70%), injection site tenderness (greater than 50%), decreased appetite (greater than 40%), decreased sleep (greater than 40%), increased sleep (greater than 40%), fever (greater than 20%), injection site redness (greater than 20%), and injection site swelling (greater than 20%).
- In children aged 5 through 17 years, the most commonly reported solicited adverse reactions (greater than 5%) were injection site tenderness (greater than 80%), injection site redness (greater than 30%), injection site swelling (greater than 30%), irritability (greater than 20%), decreased appetite (greater than 20%), increased sleep (greater than 20%), fever (greater than 5%), and decreased sleep (greater than 5%).
- In adults aged 18 years and older, the most commonly reported solicited adverse reactions (greater than 5%) were pain at the injection site (greater than 50%), fatigue (greater than 30%), headache (greater than 20%), muscle pain (greater than 20%), joint pain (greater than 10%), decreased appetite (greater than 10%), injection site redness (greater than 10%), injection site swelling (greater than 10%), limitation of arm movement (greater than 10%), vomiting (greater than 5%), fever (greater than 5%), chills (greater than 5%), and rash (greater than 5%).

Pneumococcal 15-valent Conjugate Vaccine (PCV15, Vaxneuvance)

Pneumococcal 15-valent conjugate vaccine is available as Vaxneuvance (Merck & Co., Inc) which is supplied as a single-dose prefilled syringe of 0.5 mL suspension for intramuscular injection. In July 2021, the FDA approved Vaxneuvance for active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F in individuals 6 weeks of age and older. Protection against invasive disease is conferred mainly by opsonophagocytic killing of S. pneumoniae. Vaxneuvance induces opsonophagocytic activity against the serotypes contained in the vaccine.

FDA approval was based on data from seven randomized, double-blind clinical studies assessing safety, tolerability, and immunogenicity in adults. Clinical data showed that immune responses elicited by Vaxneuvance were non-inferior to the currently available 13-valent pneumococcal conjugate vaccine (PCV13) for the 13 shared serotypes, as assessed by opsonophagocytic activity (OPA) Geometric Mean Titers (GMTs). Additionally, immune responses for Vaxneuvance were superior to PCV13 for shared serotype 3 and for the two serotypes unique to Vaxneuvance, 22F and 33F. In the pivotal Phase 3 PNEU-AGE (V114-019) study, superiority for Vaxneuvance relative to PCV13 was based on statistically significantly greater OPA GMT ratios for serotypes 22F [GMT Ratio 32.52 (95% Confidence Interval (CI) 25.87, 40.88)] and 33F [GMT Ratio 7.19 (95% CI 6.13, 8.43)], as well as for the key secondary objective assessing serotype 3 [GMT Ratio 1.62 (95% CI 1.40, 1.87)]. Randomized controlled trials assessing the clinical efficacy of Vaxneuvance compared to PCV13 have not been conducted (Merck, 2021a).

In 2022, the label for Vaxneuvance was expanded to include children and adolescence. FDA approval was based on double-blind, active comparator-controlled studies that randomized infants, children and adolescents to receive Vaxneuvance or Prevnar 13 in a 4-dose series or receiving catch-up vaccination. Vaxneuvance was found to be noninferior to Prevnar 13, and for the catch-up vaccination study, Vaxneuvance elicited immune responses, as assessed by serotype-specific IgG GMCs at 30 days following the last dose of vaccine, in children 7 months through 17 years of age that were numerically similar to Prevnar 13 for the shared serotypes and higher than Prevnar 13 for the unique serotypes 22F and 33F. Within each age cohort, serotype-specific IgG GMCs at 30 days following the last dose of vaccine were numerically similar between the vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the 2 unique serotypes (Merk, 2022).

Some individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to Vaxneuvance.

There are no adequate and well-controlled studies of Vaxneuvance in pregnant women. Available data on Vaxneuvance administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. In addition, human data are not available to assess the impact on milk production, its presence in breast milk, or its effects on the breastfed child.

Warnings and precautions in the prescribing information state that apnea following intramuscular vaccination has been observed in some infants born prematurely. A decision about when to administer Vaxneuvance to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

Per the label, the most commonly reported solicited adverse reactions include the following:

- In children vaccinated with a 4-dose series at 2, 4, 6 and 12 through 15 months of age, provided as a range across the series, were: irritability (57.3% to 63.4%), somnolence (24.2% to 47.5%), injection-site pain (25.9% to 40.3%), fever ≥38.0°C (13.3% to 20.4%), decreased appetite (14.1% to 19.0%), injection-site induration (13.2% to 15.4%), injection-site erythema (13.7% to 21.4%) and injection-site swelling (11.3% to 13.4%).
- In children and adolescents 2 through 17 years of age vaccinated with a single dose were: injection-site pain (54.8%), myalgia (23.7%), injection-site swelling (20.9%), injection-site erythema (19.2%), fatigue (15.8%), headache (11.9%) and injection-site induration (6.8%).
- In individuals 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%) and arthralgia (12.7%).

- In individuals 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%) and arthralgia (7.7%).

Pneumococcal 20-valent Conjugate Vaccine (PCV20, Prevnar 20)

Pneumococcal 20-valent conjugate vaccine is available as Prevnar 20 (Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc) and is supplied in a single-dose pre-filled syringe of 0.5 mL suspension for intramuscular injection. Prevnar 20 was FDA approved in April 2023 for active immunization for the prevention of the following:

- invasive pneumococcal disease (IPD) caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in individuals 6 weeks of age and older;
- otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age;
- pneumonia caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in individuals 18 years of age and older.

Per the label, the indication for the prevention of pneumonia caused by S. pneumoniae serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F in individuals 18 years of age and older is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA) assay. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Prevnar 20 includes capsular polysaccharide conjugates for the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) already included in Prevnar 13 (pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} protein]). The vaccine also contains capsular polysaccharide conjugates for seven additional serotypes (8, 10A, 11A, 12F, 15B, 22F and 33F) that cause invasive pneumococcal disease (IPD) and have been associated with high case-fatality rates, antibiotic resistance, and/or meningitis (Pfizer, 2021).

The FDA approved Prevnar 20 for the prevention of invasive disease and pneumonia in adults 18 years of age and older in June 2021. FDA approval was based on evidence from Pfizer's clinical program in adults, including Phase 1 and 2 trials, and three Phase 3 trials (NCT03760146, NCT03828617, and NCT03835975) describing the safety and evaluating the immunogenicity of the vaccine. More than 6,000 adult subjects 18 years and older participated in the three Phase 3 trials, including adults 65 years of age and older, vaccine-naïve adults, and adults with prior pneumococcal vaccination (Pfizer, 2021).

FDA approval for use in children is based on results demonstrated in phase 2 and phase 3 clinical trials, including three core phase 3 pediatric studies that contributed to the data on the safety, tolerability, and immunogenicity of Prevnar 20. For more information on trial outcomes, see the section on Clinical Studies in Prevnar 20 - Full Prescribing Information (Pfizer, 2023, Wyeth Pharmaceuticals, 2023).

There are no adequate and well-controlled studies of Prevnar 20 in pregnant women. It is not known whether Prevnar 20 is excreted in human milk.

Prevnar 20 is administered to children as a 4-dose immunization series at 2, 4, 6, and 12 through 15 months of age. For adults 18 years of age and older, Prevnar 20 is administered as a single dose.

The effectiveness of Prevnar 20 for the prevention of pneumonia has not been established in individuals younger than 18 years of age. In addition, the safety and effectiveness of Prevnar 20 in individuals younger than 6 weeks of age have not been established (Wyeth Pharmaceuticals, 2023).

Per the label, Prevnar 20 is contraindicated for those who are allergic to any component of Prevnar 20 or to diphtheria toxoid. Warnings and precautions include apnea following intramuscular vaccination which has been observed in some infants born prematurely, and that decisions about when to administer Prevnar 20 to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

Adverse reactions include the following:

- In individuals 2, 4, 6, and 12 through 15 months of age vaccinated with a 4-dose schedule, the most commonly reported solicited adverse reactions greater than 10% were irritability (greater than 60%), pain at the injection site (greater than 30%), drowsiness (greater than 30%), decreased appetite and injection site redness (greater than 20%), injection site swelling (greater than 10%), and fever (greater than 10%).
- In individuals 15 months through 17 years of age vaccinated with a single dose, the most commonly reported solicited adverse reactions greater than 10% were irritability (greater than 60% in individuals less than 2 years of age), pain at the injection site (greater than 50%), drowsiness (greater than 40% in individuals less than 2 years of age), fatigue and muscle pain (greater than 20% in individuals 2 years of age and older), decreased appetite (greater than 20% in individuals less than 2 years of age), injection site swelling and injection site redness (greater than 10%) and headache (greater than 10% in individuals 5 years of age and older), and fever (greater than 10% in individuals less than 2 years of age).

- In individuals 18 through 59 years of age, the most commonly reported solicited adverse reactions greater than 10% were pain at the injection site (greater than 70%), muscle pain (greater than 50%), fatigue (greater than 40%), headache (greater than 30%), and arthralgia and injection site swelling (greater than 10%).
- In individuals 60 years of age and older, the most commonly reported solicited adverse reactions greater than 10% were pain at the injection site (greater than 50%), muscle pain and fatigue (greater than 30%), headache (greater than 20%), and arthralgia (greater than 10%).

Pneumococcal 21-valent Conjugate Vaccine (PCV21, Capvaxive)

Pneumococcal 21-valent conjugate vaccine is available as Capvaxive (Merck & Co., Inc.) and is supplied in a single-dose pre-filled syringe of 0.5 mL suspension for intramuscular injection. Capvaxive was FDA approved in June 2024 for active immunization for the prevention of the following:

- Invasive disease caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older;
- Pneumonia caused by S. pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

The indication for the prevention of pneumonia caused by S. pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B is approved under accelerated approval based on immune responses as measured by opsonophagocytic activity (OPA). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Capvaxive includes 8 serotypes not covered by other currently approved pneumococcal vaccines; of which, those serotypes were responsible for approximately 27% of invasive pneumococcal disease (IPD) cases in adults 50 years of age and older and approximately 30% in adults 65 years of age and older, based on 2018-2021 CDC data (Merck, 2024b).

Capvaxive was FDA approved on June 17, 2024, for the prevention of invasive pneumococcal disease and pneumococcal pneumonia in adults. FDA approval was based on data that included Phase 3 clinical studies designed to evaluate the safety and immunogenicity of Capvaxive in a variety of adult populations, which include the following (Merck, 2024c):

- Vaccine-naïve adults : STRIDE-3 (NCT05425732) is a double-blind, Phase 3 study which evaluated Capvaxive compared to PCV20 in individuals 18 years of age and older who had not previously received a pneumococcal conjugate vaccine. Participants 50 years of age and older were enrolled in cohort 1 (n=2,362), and participants 18 through 49 years of age were enrolled in cohort 2 (n=300). Participants were randomized to receive a single dose of either Capvaxive or PCV20.
    - In adults 50 years of age and older (cohort 1), Capvaxive was non-inferior to PCV20 for the 10 serotype polysaccharides shared with both vaccines (3, 6A, 7F, 8, 10A, 11A, 12F, 19A, 22F, 33F), as assessed by serotype-specific OPA geometric mean titers (GMTs) at 1 month post-vaccination;
        - Capvaxive was superior to PCV20 for 10 of 11 serotype polysaccharides included in Capvaxive but not in PCV20 (9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31, 35B), as assessed by serotype-specific OPA GMTs 1 month post-vaccination and the proportions of patients with a greater than or equal to four-fold increase in OPA from pre-vaccination to 1 month post-vaccination;
        - Immune responses were observed for serotype 15C in participants receiving Capvaxive but did not meet criteria for statistical significance.
    - In individuals 18 through 49 years of age (cohort 2), Capvaxive elicited non-inferior immune responses (immuno-bridged) compared to individuals 50 through 64 years of age, as assessed by serotype-specific OPA GMTs 1 month post-vaccination;
    - Across both cohorts, Capvaxive had a safety profile comparable to PCV20.

- Co-administration of Capvaxive with quadrivalent influenza vaccine (QIV) : STRIDE-5 (NCT05526716) is a randomized, double-blind, Phase 3 study which evaluated Capvaxive when administered concomitantly or sequentially (30 days later) with QIV in adults 50 years of age and older (n=1,080). Results from the study include:
    - For the primary immunogenicity endpoints, Capvaxive administered concomitantly with QIV was non-inferior to Capvaxive administered sequentially with QIV for 20 of 21 serotypes in Capvaxive (as assessed by OPA GMTs at 1 month post-vaccination), as well as for three of four influenza strains in QIV (as assessed by hemagglutination inhibition (HAI) GMTs at 1 month post-vaccination);
    - The rates and severity of solicited systemic adverse reactions and solicited local adverse reactions at the CAPVAXIVE injection site were similar when CAPVAXIVE was administered with or without inactivated QIV.

- Vaccine-experienced adults : STRIDE-6 (NCT05420961) is a randomized descriptive Phase 3 study which evaluated Capvaxive in individuals 50 years of age and older who had previously received a pneumococcal vaccine at least one year before enrollment. Participants were enrolled into one of three cohorts based on their previous pneumococcal vaccination history (cohort 1: PPSV23 [pneumococcal 23-valent polysaccharide vaccine], cohort 2: PCV13 [pneumococcal 13-valent conjugate vaccine], or cohort 3: PPSV23 followed by or preceded by PCV13, PPSV23 preceded by PCV15 [pneumococcal 15-valent conjugate vaccine], or PCV15 alone). Participants in cohort 1 were randomized to receive Cavaxive (n=231) or PCV15 (n=119), participants in cohort 2 were randomized to receive Capvaxive (n=176) or PPSV23 (n=85), and participants in cohort 3 were allocated to receive Capvaxive (n=106). In each of the 3 cohorts, serotype-specific OPA GMTs and the proportion of individuals with ≥4-fold rise in OPA responses from baseline to 1-month post-vaccination were assessed. Results from the study include:
    - In cohort 1, CAPVAXIVE elicited OPA responses that were comparable to PCV15 for the 6 common serotypes, and higher for the 15 unique serotypes and serotype 15B;
    - In cohort 2, CAPVAXIVE elicited OPA responses comparable to PPSV23 for the 12 common serotypes and serotype 15B, and higher for the 9 unique serotypes;
    - OPA responses to CAPVAXIVE were similar across the 3 cohorts of participants who previously received one or more pneumococcal vaccines;
    - Capvaxive had a safety profile comparable to both PCV15 and PPSV23.

The most commonly reported (greater than 10%) solicited adverse reactions:

- In individuals 18 through 49 years of age were: injection-site pain (73.1%), fatigue (36.0%), headache (27.5%), myalgia (16.4%), injection-site erythema (13.8%), and injection-site swelling (13.3%).
- In individuals 50 years of age and older were: injection-site pain (41.2%), fatigue (19.7%), and headache (11.0%).

There are no adequate and well-controlled studies of Capvaxive in pregnant individuals. Data on Capvaxive administered to pregnant individuals are insufficient to inform vaccine-associated risks in pregnancy.

The safety and effectiveness of Capvaxive in individuals younger than 18 years of age have not been established.

Adults Aged 65 Years and Older

A randomized placebo-controlled trial of 13-valent pneumococcal conjugate vaccine was conducted in about 84,500 adults aged 65 years and older, with no particular risk factors. Four years on average after vaccination, there was no reduction in either mortality or the overall incidence of community-acquired pneumonia. It was necessary to vaccinate about 1,000 individuals in order to prevent 1 case of vaccine-type pneumococcal pneumonia during the 4-year follow-up period (No authors listed, 2016).

In 2019, the Centers for Disease Control and Prevention (CDC) updated the recommendations of the Advisory Committee on Immunization Practices for use of 13-valent pneumococcal conjugate vaccine (PCV13). PCV13 vaccination is no longer routinely recommended for all adults aged 65 years and older. Instead, shared clinical decision-making for PCV13 use is recommended for persons in this age group who do not have an immunocompromising condition, CSF leak, or cochlear implant and who have not previously received PCV13. If a decision to administer PCV13 is made, it should be administered before PPSV23. The recommended intervals between pneumococcal vaccines remain unchanged for adults without an immunocompromising condition, CSF leak, or cochlear implant (≥1 year between pneumococcal vaccines, regardless of the order in which they were received). PCV13 and PPSV23 should not be co-administered. ACIP continues to recommend PCV13 in series with PPSV23 for adults aged ≥19 years (including those aged ≥65 years) with immunocompromising conditions, CSF leaks, or cochlear implants (Matanock et al., 2019).

All adults 65 years or older should receive 1 dose of PPSV23. Anyone who received any doses of PPSV23 before age 65 should receive 1 final dose of the vaccine at age 65 or older. Administer this last dose at least 5 years after the prior PPSV23 dose (CDC, 2019; Matanock et al., 2019).

On October 20, 2021, the CDC's ACIP updated the pneumococcal vaccine recommendations for adults aged 65 years and older. See ACIP recommendations section.

On June 27, 2024, the CDC's ACIP updated the pneumococcal vaccine recommendations for adults aged 65 years and older. See ACIP recommendations section.

Elective Splenectomy

An UpToDate review on "Prevention of sepsis in the asplenic patient" (Pasternack, 2016) states the following:

If a patient has anatomic or functional asplenia, we recommend immunization with pneumococcal, meningococcal, and Haemophilus influenzae type b vaccine.

If a patient will be undergoing elective splenectomy, we recommend that the pneumococcal, meningococcal, and Haemophilus influenzae vaccines be administered at least 14 days prior to surgery. If it is not possible to administer these vaccines prior to splenectomy, they can be given after the 14th post-operative day.

Immune Response to Vaccines in Rheumatoid Arthritis

Hua et al (2014) evaluated the current literature on the impact of rheumatoid arthritis (RA) treatments on the humoral response to pneumococcal and influenza vaccines. These investigators systematically searched the literature for studies evaluating the immune response to vaccines in RA patients receiving methotrexate (MTX) and/or biologic agents. The effectiveness of vaccination, assessed by the response rate based on increased antibody titers before and 3 to 6 weeks after vaccination, was extracted by one investigator and verified by another. A total of 12 studies were included. Rheumatoid arthritis patients mainly received MTX, anti-tumor necrosis factor alpha (anti-TNFα), or rituximab (RTX). Influenza vaccination response was reduced for RTX (43 patients; pooled odds ratio [OR] 0.44 [95 % CI: 0.17 to 1.12] for H1N1, OR 0.11 [95 % CI: 0.04 to 0.31] for H3N2, and OR 0.29 [95 % CI: 0.10 to 0.81] for B) but not for anti-TNFα (308 patients; OR 0.93 [95 % CI: 0.36 to 2.37] for H1N1, OR 0.79 [95 % CI: 0.34 to 1.83] for H3N2, and OR 0.79 [95 % CI: 0.37-1.70] for B). For MTX, results differed depending on the method of analysis (222 patients; OR 0.35 [95 % CI: 0.18 to 0.66] for at least 2 strains, ORs were close to 1.0 in the single strain analysis). Pneumococcal vaccination response was reduced for 139 patients receiving MTX compared with controls (OR 0.33 [95 % CI: 0.20 to 0.54] for serotype 6B and OR 0.58 [95 % CI: 0.36 to 0.94] for 23F) but not for anti-TNFα (258 patients; OR 0.96 [95 % CI: 0.57 to 1.59] for 6B and OR 1.20 [95 % CI: 0.57 to 2.54] for 23F). For RTX, the response was reduced (88 patients; OR 0.25 [95 % CI: 0.11 to 0.58] for 6B and OR 0.21 [95 % CI: 0.04 to 1.05] for 23F). The authors concluded that MTX decreased humoral response to pneumococcal vaccination and may impair response to influenza vaccination. The immune response to both vaccines was reduced with RTX; but not with anti-TNFα therapy in RA patients.

Intra-Nasal Pneumococcal Vaccine

Li and colleagues (2018) stated that Streptococcus pneumoniae is a major respiratory tract pathogen causing high levels of mortality and morbidity in infants and the elderly. In spite of the multitude of capsular polysaccharide vaccines used to guard against pneumococcal disease, fatal pneumococcal disease remains epidemic. Immunization with pneumococcal surface protein A (PspA), a highly immunogenic surface protein present in all strains of S. pneumoniae, can elicit protection against deadly pneumococcal infection. These investigators had previously evaluated PspA in systemic vaccination. However, the mucosal immune system, as a first-line of defense against respiratory infection, plays the most important role against the invasion of S. pneumoniae. In this study, these researchers employed bacterium-like particles (BLPs) as an adjuvant for a PspA mucosal vaccine. The BLPs served as a carrier for PspA proteins bound to their surface. Mice were immunized intra-nasally with the PspA-BLP pneumococcal vaccine consisting of PspA3 from pneumococcal family 2. Not only did the immunized mice show a high level of serum IgG antibodies but also a high level of SIgA antibodies in the respiratory tract. After immunization with the PspA3-BLP vaccine, the mice were broadly protected against fatal intra-nasal challenge with homologous and heterogeneous pneumococcal strains of different PspA families regardless of serotype, and the colony count was notably decreased in the lungs. The authors concluded that the PspA3-BLP pneumococcal vaccine has the potential to serve as a novel mucosal vaccine to enhance both systemic and mucosal immune responses to this disease.

Yu and associates (2018) vaccinated mice via the subcutaneous (s.c.) route with a systemic vaccine that is a mixture of fusion protein PsaA-PspA23 and a single protein, PspA4, with aluminum hydroxide as an adjuvant. As a comparison, mice were immunized intra-nasally with a mucosal vaccine that is a mixture of PspA2-PA-BLP (where PA is protein anchor and BLP is bacterium-like particle) and PspA4-PA-BLP, via the intra-nasal (i.n.) route. The 2 immunization processes were followed by challenge with Streptococcus pneumoniae bacteria from 2 different PspA families. Specific IgG titers in the serum and specific IgA titers in the mucosa were determined following immunizations. Bacterial loads and survival rates after challenge were compared. Both the systemic vaccine and the mucosal vaccine induced a significant increase of IgG against PspAs. Only the mucosal vaccine also induced specific IgA in the mucosa. The 2 vaccines provided protection, but each vaccine showed an advantage. The authors concluded that the systemic vaccine induced higher levels of serum antibodies, whereas the mucosal vaccine limited the bacterial load in the lung and blood. These researchers stated that co-immunizations with the 2 types of vaccines may be implemented in the future.

Lu and co-workers (2019) applied BLPs as an adjuvant for the development of a PspA mucosal vaccine, in which the PspA protein was displayed on the surface of BLPs. Intra-nasal immunization with the PspA-BLP pneumococcal vaccine, comprised of PspA2 from pneumococcal family 1 and PspA4 from pneumococcal family 2, not only induced a high level of serum IgG antibodies but also a high level of mucosal SIgA antibodies. Analysis of binding of serum antibodies to intact bacteria showed a broad coverage of binding to pneumococcal strains expressing PspA from clade 1 to 5. Immunization with the PspA-BLP vaccine conferred protection against fatal intranasal challenge with both PspA family 1 and family 2 pneumococcal strains regardless of serotype. The authors concluded that the PspA-BLP pneumococcal vaccine was demonstrated to be a promising strategy for mucosal immunization to enhance both systemic and mucosal immune responses.

Pneumococcal Vaccination in Adult Solid Organ Transplant Recipients

Dendle and colleagues (2018) summarized the current literature relating to pneumococcal vaccination in adult solid organ transplant (SOT) recipients, who are at risk of invasive pneumococcal disease (IPD) with its attendant high morbidity and mortality. The effect of the pneumococcal polysaccharide vaccine has been examined in several small cohort studies in SOT recipients, most of which were kidney transplant recipients. The outcomes for these studies have been laboratory sero-responses or functional antibody titers. Overall, in most of these studies the transplant recipients were capable of generating measurable serological responses to pneumococcal vaccination but these responses were less than those of healthy controls. A mathematical model estimated the effectiveness of polysaccharide vaccination in SOT recipients to be 1/3 less than those of patients with HIV. The evidence for the efficacy of the pneumococcal conjugate vaccine in SOT is based on a small number of RCTs in liver and kidney transplant recipients. These trials demonstrated that SOT recipients mounted a serological response following vaccination; however there was no benefit to the use of prime boosting (conjugate vaccine followed by polysaccharide vaccine). Currently there are no randomized studies investigating the clinical protection rate against IPD after pneumococcal vaccination by either vaccine type or linked to vaccine titers or other responses against pneumococcus. Concerns that vaccination may increase the risk of adverse allo-responses such as rejection and generation of donor specific antibodies are not supported by studies examining this aspect of vaccine safety. The authors concluded that pneumococcal vaccination is a potentially important strategy to reduce IPD in SOT recipients and is associated with excellent safety. Current international recommendations are based on expert opinion from conflicting data, hence there is a clear need for further high-quality studies in this high-risk population examining optimal vaccination regimens. Such studies should focus on strategies to optimize functional immune responses.

Pneumococcal Vaccine on Mortality and Cardiovascular Outcomes

Jaiswal et al (2022) stated that various studies have suggested the possible cardiovascular (CV) protective effects of the PCV. In a meta-analysis, these researchers examined the association between recipients of PCV with mortality and CV outcomes among patients with and without established cardiovascular disease. They carried out a systematic literature search in PubMed, Embase, and Scopus for studies examining the effect of PCV on mortality and CV outcomes. A total of 15 studies with 347,444 patients were included in the meta-analysis: 111,784 patients received PCV (32 %), and 235,660 patients were in the unvaccinated group (68 %). Recipients of PCV were associated with decreased all-cause mortality (HR, 0.76 (95 % CI: 0.66 to 0.87), $p < 0.001$). PCV was associated with a decrease in the incidence of myocardial infarction (MI) (HR, 0.73 (95 % CI: 0.56 to 0.96), $p = 0.02$), without significant reduction in CV mortality (HR, 0.87 (95 % CI: 0.72 to 1.07), $p = 0.18$) and stroke (HR, 1.01 (95 % CI: 0.93 to 1.10), $p = 0.82$). The authors concluded that PCV was associated with decreased risk of all-cause mortality and MI. Moreover, these researchers stated that future RCTs are needed to confirm benefits associated with receipt of PCV.

In a systematic review, Addario et al (2023) examined the impact of vaccination against influenza, shingles, and pneumococcus on the incidence on the risk of CV events in the elderly. This protocol was developed in accordance with PRISMA guidelines. These investigators carried out a literature search and identified all relevant studies published regarding the matter up to September 2022. These investigators retrieved 38 studies (influenza vaccine = 33, PCV = 5, and zoster vaccine = 2). A total of 28 and 2 studies have shown that influenza vaccine and PCV significantly reduced the risk of CV disease in the elderly. Furthermore, repeated influenza vaccination showed a consistent and dose-dependent protective effect against acute coronary syndromes and stroke. Moreover, dual influenza and PC vaccination was associated with lower risks of some CV events (stroke, congestive heart failure [CHF], ischemic heart disease, and MI). However, the impact of PCV13 on CV events has not been studied, nor has the currently recommended vaccination schedule (PCV13 + PPV23). As for herpes zoster vaccination, only the protective effect against stroke has been studied with the live attenuated herpes zoster vaccine, but no studies have been carried out with the recombinant subunit herpes zoster vaccine. The authors concluded that this review outlined the benefits of the afore-mentioned vaccines beyond their preventive action on infectious diseases. It is intended for healthcare professionals who wish to inform and advise their elderly patients.

Prevention of Acute Exacerbations of COPD in Persons with Moderate, Severe, or Very Severe COPD

The American College of Chest Physicians and Canadian Thoracic Society guideline on "Prevention of acute exacerbations of COPD" (Criner et al, 2015) states that in patients with COPD, the panel suggests administering the 23-valent pneumococcal vaccine as part of overall medical management; but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Prevention of Acute Otitis Media

Fortanier and colleagues (2014) stated that acute otitis media (AOM) is a very common respiratory infection in early infancy and childhood. The marginal benefits of antibiotics for AOM in low-risk populations in general, the increasing problem of bacterial resistance to antibiotics and the huge estimated direct and indirect annual costs associated with otitis media (OM) have prompted a search for effective vaccines to prevent AOM. These researchers examined the effect of pneumococcal conjugate vaccines (PCVs) in preventing AOM in children up to 12 years of age. They searched CENTRAL (2013, Issue 11), MEDLINE (1995 to Week 3, November 2013), EMBASE (1995 to December 2013), CINAHL (2007 to December 2013), LILACS (2007 to December 2013) and Web of Science (2007 to December 2013). Randomized controlled trials (RCTs) of PCVs to prevent AOM in children aged 12 years or younger, with a follow-up of at least 6 months after vaccination were selected for analysis. Two review authors independently assessed trial quality and extracted data. They included 11 publications of 9 RCTs (n = 48,426

children, range of 74 to 37,868 per study) of 7- to 11-valent PCV (with different carrier proteins). Five trials (n = 47,108) included infants, while 4 trials (n = 1,318) included children aged 1 to 7 years that were either healthy (1 study, n = 264) or had a previous history of upper respiratory tract infection (URTI), including AOM. These researchers judged the methodological quality of the included studies to be moderate to high. There was considerable clinical diversity between studies in terms of study population, type of conjugate vaccine and outcome measures. The authors therefore refrained from pooling the results. In 3 studies, the 7-valent PCV with CRM197 as carrier protein (CRM197-PCV7) administered during early infancy was associated with a relative risk reduction (RRR) of all-cause AOM ranging from -5 % in high-risk children (95 % CI: -25 % to 12 %) to 7 % in low-risk children (95 % CI: 4 % to 9 %). Another 7-valent PCV with the outer membrane protein complex of Neisseria meningitidis (N. meningitidis) serogroup B as carrier protein, administered in infancy, did not reduce overall AOM episodes, while a precursor 11-valent PCV with Haemophilus influenzae (H. influenzae) protein D as carrier protein was associated with a RRR of all-cause AOM episodes of 34 % (95 % CI: 21 % to 44 %). A 9-valent PCV (with CRM197 carrier protein) administered in healthy toddlers was associated with a RRR of (parent-reported) OM episodes of 17 % (95 % CI: -2 % to 33 %). CRM197-PCV7 followed by 23-valent pneumococcal polysaccharide vaccination administered after infancy in older children with a history of AOM showed no beneficial effect on first occurrence and later AOM episodes. In a study in older children with a previously diagnosed respiratory tract infection, performed during the influenza season, a trivalent influenza vaccine combined with placebo (TIV/placebo) led to fewer all-cause AOM episodes than vaccination with TIV and PCV7 (TIV/PCV7) when compared to hepatitis B vaccination and placebo (HBV/placebo) (RRR 71 %, 95 % CI: 30 % to 88 % versus RRR 57 %, 95 % CI: 6 % to 80 %, respectively) indicating that CRM197-PCV7 after infancy may even have negative effects on AOM. The authors concluded that based on current evidence of the effects of PCVs for preventing AOM, the licensed 7-valent CRM197-PCV7 has modest beneficial effects in healthy infants with a low baseline risk of AOM. Administering PCV7 in high-risk infants, after early infancy and in older children with a history of AOM, appears to have no benefit in preventing further episodes. Currently, several RCTs with different (newly licensed, multivalent) PCVs administered during early infancy are ongoing to establish their effects on AOM. Results of these studies may provide a better understanding of the role of the newly licensed, multivalent PCVs in preventing AOM. Also the impact on AOM of the carrier protein D, as used in certain pneumococcal vaccines, needs to be further established.

In a systematic review and meta-analysis, Wannarong et al (2023) examined the effect of the pneumococcal vaccine (PCV) toward the surgical management and complications of OM. Data sources included Medline, Embase, PubMed, Scopus, and clinicaltrial.gov. These investigators carried out a systematic search using a combination of keywords and standardized terms regarding PCV and surgical management or complications of OM. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, studies were screened by 3 independent reviewers. Risk of bias assessment, followed by meta-analysis in only RCTs was carried out; vaccine efficacy (VE) and 95 % CI were reported. Of the 2,649 abstracts reviewed, 27 studies were included in the qualitative analysis and were categorized into 6 outcomes: tympanostomy tube insertion, otitis media with effusion (OME), mastoiditis, spontaneous tympanic membrane (TM) perforation, recurrent AOM, and severe AOM. A total of 15 studies were included in the meta-analysis to examine the rate of tympanostomy tube insertion, OME, and recurrent AOM. PCV was significantly more effective in lowering the rate of tympanostomy tube insertion (VE, 22.2 %; 95 % CI: 14.6 to 29.8) and recurrent AOM (VE, 10.06 %; 95 % CI: 7.46 to 12.65) when compared with the control group, with no significant difference in reducing the incidence of OME. The qualitative analysis revealed that PCV had effectiveness in preventing severe AOM and spontaneous TM perforation but the effect on mastoiditis remained unclear. The authors concluded that the PCV was effective in reducing the rate of tympanostomy tube insertion and the incidence of recurrent AOM with a non-significant effect in preventing OME in children.

Quantitation of Streptococcus Pneumoniae Antibody (IgG)

Orange et al (2006) stated that human immunoglobulin prepared for intravenous administration (IVIG) has many important applications in the treatment of disease. Some of these are in diseases for which acceptable treatment alternatives do not exist. These investigators examined the evidence underlying a wide variety of IVIG uses and made specific recommendations on the basis of these data. The authors stated that deficient antibody production is usually defined by decreased immunoglobulin concentrations, or a significant inability to respond with IgG antibody production following antigenic challenge, or both. Reduced levels of serum immunoglobulin in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (i.e., patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both) is a clear indication for IgG replacement.

Lawrence and Borish (2022) examined the pitfalls associated with defining exactly what constitutes an "impaired" antibody response to polysaccharide antigens and the importance of documenting actual pyogenic infections before making a diagnosis of an immune deficiency. Specific antibody deficiency is an immune deficiency defined by the presence of normal quantitative levels of immunoglobulins, but impaired antibody responses to polysaccharide antigens, in patients presenting with frequent oto-sino-pulmonary infections with pyogenic bacteria. These investigators searched PubMed using the following keywords: specific antibody deficiency, pneumococcal vaccination, Salmonella vaccination, and infectious sinusitis. This review focused on key studies that have been utilized to define what constitutes a "normal" humoral immune response to pneumococcal and Salmonella vaccination in healthy subjects as well as on published studies defining current expert opinion. Published studies revealed wide variability in response to pneumococcal vaccination in healthy individuals, making it difficult to define what constitutes an abnormal response. Moreover, these challenges were exacerbated by marked laboratory variability in reporting results. The authors concluded that clinical examinations in individuals with self-reported recurrent acute sinusitis or lower respiratory infections need to document an infectious etiology with pyogenic bacteria and must rule out an underlying primary airway inflammatory disorder before consideration is made regarding the presence of an immune deficiency. Furthermore,

decision-making regarding diagnosis and treatment of patients who were examined for humoral immunodeficiency should not hinge solely on the strict application of defined cut-offs for "normal" response to a single polysaccharide vaccine, but rather a global assessment of humoral immune function in the context of the clinical presentation.

An UpToDate chapter on “Pneumococcal pneumonia in patients requiring hospitalization” (Musher and Tuomanen, 2024) stated that “A variety of other tests have been used to diagnose pneumococcal pneumonia, including immunoglobulin (Ig)G antibodies to capsular polysaccharides, the autolysin LytA, and pneumolysin, and several quantitative PCR assays. None is well validated or routinely used”.

Reducing Morbidity and Mortality in Persons with Cystic Fibrosis

Burgess and Southern (2014) stated that invasive pneumococcal disease is associated with significant mortality and many countries have introduced routine pneumococcal vaccination into their childhood immunization programs. While pneumococcal disease in cystic fibrosis (CF) is uncommon, pneumococcal immunization may offer some protection against pulmonary exacerbations caused by this pathogen. In the USA and UK pneumococcal vaccination is currently recommended for all children and adults with CF. In a Cochrane review, these investigators evaluated the effectiveness of pneumococcal vaccines in reducing morbidity in people with CF. They searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Cystic Fibrosis Trials Register, which comprises references identified from comprehensive electronic database searches and hand-searches of relevant journals and abstract books of conference proceedings. In addition, the pharmaceutical manufacturers of the polysaccharide and conjugate pneumococcal vaccines were approached. Date of the most recent search was May 15, 2014. Randomized and quasi-randomized controlled trials comparing pneumococcal vaccination (with either a polysaccharide or conjugate pneumococcal vaccine) with non-vaccination or placebo in children or adults with CF were eligible for inclusion. No relevant trials were identified. The authors concluded that as no trials were identified they could not draw conclusions on the effectiveness of routine pneumococcal immunization in people with CF in reducing their morbidity or mortality. As many countries now include pneumococcal immunization in their routine childhood vaccination schedule it is unlikely that future randomized controlled trials will be initiated. Rigorously conducted epidemiological studies may offer the opportunity to evaluate the effectiveness of pneumococcal vaccination in reducing morbidity and mortality in people with CF.

References

The above policy is based on the following references:

1. Adawi M, Bragazzi NL, McGonagle D, et al. Immunogenicity, safety and tolerability of anti-pneumococcal vaccination in systemic lupus erythematosus patients: An evidence-informed and PRISMA compliant systematic review and meta-analysis. Autoimmun Rev. 2019;18(1):73-92.
2. Addario A, Celarier T, Bongue B, et al. Impact of influenza, herpes zoster, and pneumococcal vaccinations on the incidence of cardiovascular events in subjects aged over 65 years: A systematic review. Geroscience. 2023;45(6):3419-3447.
3. American Academy of Pediatrics, Committee on Infectious Diseases. 1997 Red Book: Report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics; 1997.
4. American Academy of Pediatrics, Committee on Infectious Diseases. Policy statement: Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics. 2000;106(2 Pt 1):362-366.
5. American Academy of Pediatrics, Committee on Infectious Diseases. Technical report: Prevention of pneumococcal infections, including use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. Pediatrics. 2000;106(2 Pt 1):367-376.
6. American College of Physicians Task Force on Adult Immunization and Infectious Disease Society of America. Guide for Adult Immunization. 3rd ed. Philadelphia, PA: American College of Physicians; 1994.
7. Anderson HH. Pneumococcal vaccination in elderly and at-risk patients. Am Fam Physician. 1998;57(10):2346.
8. Bennett, NM, Centers for Disease Control (CDC), Advisory Committee on Immunization Practices (ACIP). 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). MMWR Morb Mortal Wkly Rep. 2012;61(40):816-819.
9. Berman-Rosa M, O'Donnell S, Barker M, Quach C. Efficacy and effectiveness of the PCV-10 and PCV-13 vaccines against invasive pneumococcal disease. Pediatrics. 2020;145(4):e20190377.
10. Beutels P, Van Damme P, Oosterhuis-Kafeja F. Pneumococcal vaccination of children in Belgium. KCE Reports 33. Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE); 2006.
11. Brown A. Prevnar: A pneumococcal conjugate vaccine for infants and young children. Issues in Emerging Health Technologies Issue 14. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2001.
12. Burgess L, Southern KW. Pneumococcal vaccines for cystic fibrosis. Cochrane Database Syst Rev. 2014;8:CD008865.
13. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). ACIP recommendations. Atlanta, GA: CDC: reviewed August 4, 2023. Available at: https://www.cdc.gov/vaccines/acip/recommendations.html. Accessed August 18, 2023a.

14. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). ACIP recommendations. Atlanta, GA: CDC: reviewed June 28, 2024a. Available at: https://www.cdc.gov/vaccines/acip/recommendations.html. Accessed July 16, 2024.
15. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). ACIP shared clinical decision-making recommendations. Atlanta, GA: CDC; reviewed September 29, 2023c. Available at: https://www.cdc.gov/vaccines/acip/acip-scdm-faqs.html. Accessed July 25, 2024.
16. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children – Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 2010;59(09):258-261.
17. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2003;52(31):739-740.
18. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Pneumococcal vaccination. ACIP provisional recommendations for use of pneumococcal vaccines. Atlanta, GA: CDC; October 2008. Available at: http://www.cdc.gov/vaccines/recs/provisional/default.htm#acip. Accessed on January 15, 2009.
19. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep. 2010;59(34):1102-1106.
20. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV7) in children aged 24-59 months who are not completely vaccinated. MMWR Morb Mortal Wkly Rep. 2008;57(13):343-344.
21. Centers for Disease Control and Prevention (CDC). Pneumococcal vaccination for cochlear implant recipients. MMWR Morb Mortal Wkly Rep. 2002;51(41):931.
22. Centers for Disease Control and Prevention (CDC). Pneumococcal vaccine recommendations [website]. October 26, 2024b. Available at: https://www.cdc.gov/pneumococcal/hcp/vaccine-recommendations/index.html. Accessed January 22, 2025.
23. Centers for Disease Control and Prevention (CDC). Pneumococcal vaccine timing for adults. Atlanta, GA: CDC; March 16, 2020. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf. Accessed April 14, 2020.
24. Centers for Disease Control and Prevention (CDC). Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2000;49(RR-9):1-35.
25. Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1997;46(RR-8):1-12.
26. Centers for Disease Control and Prevention (CDC). Recommended vaccines for children [website]. June 26, 2024c. Available at: https://www.cdc.gov/pneumococcal/vaccines/children.html. Accessed January 22, 2025.
27. Centers for Disease Control and Prevention (CDC). Summary of risk-based pneumococcal vaccination recommendations [website]. October 26, 2024d. Available at: https://www.cdc.gov/pneumococcal/hcp/vaccine-recommendations/risk-indications.html. Accessed January 22, 2025.
28. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2013;62(25):521-524.
29. Centers for Disease Control and Prevention (CDC). Use of vaccines for the prevention of meningitis in persons with cochlear implants. Fact Sheet for Health Care Professionals. Atlanta, GA: CDC; July 31, 2003.
30. Centers for Disease Control and Prevention (CDC). Vaccines and preventable diseases: Pneumococcal vaccination: Summary of who and when to vaccinate. Atlanta, GA: reviewed February 13, 2023b. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html. Accessed August 21, 2023.
31. Centers for Disease Control and Prevention (CDC). Vaccines and preventable diseases: Pneumococcal vaccination: What everyone should know. Atlanta, GA: CDC; November 21, 2019. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html. Accessed April 14, 2020.
32. Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, et al. Pneumococcal vaccination during pregnancy for preventing infant infection. Cochrane Database Syst Rev. 2006;(1):CD004903.
33. Chang CC, Singleton RJ, Morris PS, Chang AB. Pneumococcal vaccines for children and adults with bronchiectasis. Cochrane Database Syst Rev. 2009;(2):CD006316.
34. Clanton M. Pneumococcal disease in United States children: Prevalence and treatment. Int J Clin Pract Suppl. 2001; 118:13-21.
35. Cordonnier C, Labopin M, Chesnel V, et al; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis. 2009;48(10):1392-1401.
36. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147(4):894-942.
37. Daum RS, Hogerman D, Rennels MB, et al. Infant immunization with pneumococcal CRM197 vaccines: Effect of saccharide size on immunogenicity and interactions with simultaneously administered vaccines. J Infect Dis.

1997;176(2):445-455.
38. Daum RS. Pneumococcal vaccines for children: An update. Pediatr Infect Dis J. 1998;17(9):823-824.
39. Davies EG, Riddington C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease. Cochrane Database Syst Rev. 2004;(1):CD003885.
40. Dendle C, Stuart RL, Mulley WR, Holdsworth SR. Pneumococcal vaccination in adult solid organ transplant recipients: A review of current evidence. Vaccine. 2018;36(42):6253-6261.
41. Eskola J, Takala AK, Kilpi TM, et al. Clinical evaluation of new pneumococcal vaccines: The Finnish approach. Dev Biol Stand. 1998;95:85-92.
42. F-D-C Reports, Inc. Wyeth to seek Prevenar otitis media indication in future submission. The Pink Sheet, November 15, 1999, p. 27.
43. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults: A meta-analysis of randomized controlled trials. Arch Intern Med. 1994;154:2666-2677.
44. Fortanier AC, Venekamp RP, Boonacker CW, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2014;4:CD001480.
45. Fortanier AC, Venekamp RP, Boonacker CW, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. Cochrane Database Syst Rev. 2019;5:CD001480.
46. Freedman M, Kroger A, Hunter P, et al. Recommended adult immunization schedule, United States, 2020. Ann Intern Med. 2020;172(5):337-347.
47. Harris G. CDC panel votes to recommend vaccine for high-risk children, based on race. Wall Street J, February 17, 2000.
48. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: A systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(7):1016-1026.
49. Jaiswal V, Ang SP, Lnu K, et al. Effect of pneumococcal vaccine on mortality and cardiovascular outcomes: A systematic review and meta-analysis. J Clin Med. 2022;11(13):3799.
50. Jansen AG, Hak E, Veenhoven RH, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2009;(2):CD001480.
51. Kausz A, Pahari D. The value of vaccination in chronic kidney disease. Semin Dial. 2004;17(1):9-11.
52. Kim DK, Bridges CB, Harriman KH; Advisory Committee on Immunization Practices. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older: United States, 2016. Ann Intern Med. 2016;164(3):184-194.
53. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: Updated recommendations of the Advisory Committee on Immunization Practices — United States, 2022. Centers for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report (MMWR). 2022a;71(4):109-117.
54. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: Updated recommendations of the Advisory Committee on Immunization Practices - United States, 2022. Centers for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report (MMWR). 2022b;71(37):1174-1181.
55. Kobayashi M, Leidner AJ, Gierke R, et al. Expanded recommendations for use of pneumococcal conjugate vaccines among adults aged ≥ 50 years: Recommendations of the Advisory Committee on Immunization Practices - United States, 2024. MMWR Weekly Report. 2025;74(1);1-8.
56. Kobayashi M, Pilishvili T, Farrar JL. Pneumococcal vaccine for adults aged ≥ 19 years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023. MMWR Recomm Rep. 2023;72(3):1-39.
57. Lardy B, Korba C, Slaughter N. Update from the extraordinary meeting of the Advisory Committee on Immunization Practices. America’s Health Insurance Plans (AHIP). Washington, DC. (Written communication, August 18, 2014).
58. Lawrence MG, Borish L. Specific antibody deficiency: Pearls and pitfalls for diagnosis. Ann Allergy Asthma Immunol. 2022;129(5):572-578.
59. Li B, Chen X, Yu J, et al. Protection elicited by nasal immunization with pneumococcal surface protein A (PspA) adjuvanted with bacterium-like particles against Streptococcus pneumoniae infection in mice. Microb Pathog. 2018;123:115-119.
60. Louden K. CDC advisory panel recommends use of newly approved pneumococcal vaccine. Medscape Medical News. New York, NY: Medscape; March, 2010. Available at: http://www.medscape.com/viewarticle/717601. Accessed on March 31, 2010.
61. Lu J, Guo J, Wang D, et al. Broad protective immune responses elicited by bacterium-like particle-based intranasal pneumococcal particle vaccine displaying PspA2 and PspA4 fragments. Hum Vaccin Immunother. 2019;15(2):371-380.
62. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and pneumonia with consolidation on x-ray in children under two years of age. Cochrane Database Syst Rev. 2009;(4):CD004977.
63. Matanock A, Lee G, Gierke R, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: Updated recommendations of the Advisory Committee on Immunization Practices. Centers for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report (MMWR). 2019;68(46):1069-1075.
64. Merck & Co., Inc. Capvaive (pneumococcal 21-valent conjugate vaccine) injectin, for intramuscular use. Prescribing Information. Rahway, NJ: Merck; June 2024a.
65. Merck & Co., Inc. CDC's ACIP unanimously recommends Merck's Capvaxive (Pneumococcal 21-valent conjugate vaccine) for pneumococcal vaccination in appropriate adults. Media News Release. Rahway, NJ: Merck; June 27, 2024b.

66. Merck & Co., Inc. Merck announces U.S. FDA approval of Vaxneuvance (pneumococcal 15-valent conjugate vaccine) for the prevention of invasive pneumococcal disease in adults 18 years and older caused by 15 serotypes. Press Release Kenilworth, NJ: Merck; July 16, 2021a.
67. Merck & Co., Inc. Pneumovax 23 (pneumococcal vaccine polyvalent) sterile, liquid vaccine for intramuscular or subcutaneous injection. Prescribing Information. Whitehouse Station, NJ: Merck; revised April 2021b.
68. Merck & Co., Inc. U.S. FDA approves Capvaxive (pneumococcal 21-valent conjugate vaccine) for prevention of invasive pneumococcal disease and pneumococcal pneumonia in adults. Media News Release. Rahway, NJ: Merck; June 17, 2024c.
69. Merck & Co., Inc. Vaxneuvance (pneumoccal 15-valent conjugate vaccine) suspension for intramuscular injection. Prescribing Information. Whitehouse Station, NJ: Merck; revised July 2021c.
70. Merck & Co., Inc. Vaxneuvance (pneumoccal 15-valent conjugate vaccine) suspension for intramuscular injection. Prescribing Information. Whitehouse Station, NJ: Merck; revised June 2022.
71. Middleton DB, Zimmerman RK, Mitchell KB. Vaccine schedules and procedures, 2003. J Fam Pract. 2003;52(1 Suppl):S36-S46.
72. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
73. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008;(1):CD000422.
74. Musher DM, Tuomanen EI. Pneumococcal pneumonia in patients requiring hospitalization. UpToDate [online serial], Waltham, MA: UpToDate; reviewed October 2024.
75. Niemin T, Kayhty H, Leroy O, et al. Pneumococcal conjugate vaccination in toddlers: Mucosal antibody response measured as circulating antibody-secreting cells and as salivary antibodies. Pediatr Infect Dis J. 1999;18(9):764-772.
76. No authors listed. Pneumococcal conjugate vaccine: Do not routinely vaccinate adults aged 65 years and older. Prescrire Int. 2016;25(172):157-158.
77. No authors listed. Pneumococcal vaccine conjugate (Wyeth-Lederle). PNCRM5, PNCRM7, PNCRM9. Drugs R D. 1999;2(3):215-219.
78. Nuorti JP, Whitney CG; Centers for Disease Control and Prevention (CDC). 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). MMWR Recomm Rep. 2010;59(RR-11):1-18.
79. Ogilvie I, Khoury AE, Cui Y, et al. Cost-effectiveness of pneumococcal polysaccharide vaccination in adults: A systematic review of conclusions and assumptions. Vaccine. 2009;27(36):4891-4904.
80. Orange JS, Hossny EM, Weiler CR, et al; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunolog. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006;117(4 Suppl):S525-5553.
81. Pasternack MS. Prevention of sepsis in the asplenic patient. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed September 2016.
82. Pfizer Inc. U.S. FDA approves Prevnar 20, Pfizer's 20-valent pneumococcal conjugate vaccine for infants and children. Press Release. New York, NY: Pfizer, 2023.
83. Pfizer Inc. U.S. FDA approves Prevnar 20, Pfizer's pneumococcal 20-valent conjugate vaccine for adults ages 18 years or older. Press Release. New York, NY: Pfizer; June 8, 2021.
84. Pierson R. U.S advisory panel recommends Prevnar 13 vaccine for enderly. Reuters, Inc. New York, NY: August 13, 2014. Available at: http://www.reuters.com/article/2014/08/13/us-pfizer-prevnar-idUSKBN0GD23I20140813. Accessed August 19, 2014.
85. Price VE, Dutta S, Blanchette VS, et al. The prevention and treatment of bacterial infections in children with asplenia or hyposplenia: Practice considerations at the Hospital for Sick Children, Toronto. Pediatr Blood Cancer. 2006;46(5):597-603.
86. Reefhuis J, Honein MA, Whitney CG, et al. Risk of bacterial meningitis in children with cochlear implants, USA 1997--2002. N Engl J Med. 2003;349(5):435--445.
87. Rennels MB, Edwards KM, Keyserling HL, et al. Safety and immunogenicity of heptavalent pneumococcal conjugated to CRM197 in United States infants. Pediatrics. 1998;101(4 Pt 1):604-611.
88. Robinson J. Efficacy of pneumococcal immunization in patients with renal disease--what is the data? Am J Nephrol. 2004;24(4):402-409.
89. Rose MA, Gruendler M, Schubert R, et al. Safety and immunogenicity of sequential pneumococcal immunization in preschool asthmatics. Vaccine. 2009;27(38):5259-5264.
90. Rosenthal, M. ACIP recommends Capvaxive for certain adults ages 19 and older. Infectious Disease Special Edition: Policy/Public Health. June 28, 2024. Available at: https://www.idse.net/. Accessed July 16, 2024.
91. Rozenbaum MH, Sanders EA, van Hoek AJ, et al. Cost effectiveness of pneumococcal vaccination among Dutch infants: Economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. BMJ. 2010;340:c2509.
92. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma. Cochrane Database Syst Rev. 2002;(1):CD002165.
93. Shinefield HR, Black S, Ray P, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. Pediatr Infect Dis J. 1999;18(9):757-763.
94. Squires SG, Spika JS. Protecting against invasive pneumococcal disease: Be wise--immunize! CMAJ. 1998;159(7):826-827.

95. Steele RW. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Clin Pediatr. 1998;37(12):760-761.
96. Stephenson J. New vaccine targets childhood pneumonia. JAMA. 1999;282(20):1905.
97. Tan TQ. Update on pneumococcal infections of the respiratory tract. Semin Respir Infect. 2002;17(1):3-9.
98. Thomas R. Preventing pneumococcal disease. Can Fam Physician. 1998;44:2180-2181, 2184-2185.
99. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2014;63(37):822-825.
100. Tseng HF, Slezak JM, Quinn VP, et al. Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men. JAMA. 2010;303(17):1699-1706.
101. U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Biologics Evaluation and Research. Vaccines and Related Biological Products Advisory Committee Meeting. Bethesda, MD: FDA; November 5, 1999.
102. U.S. Food and Drug Administration. First pneumococcal vaccine approved for infants and toddlers. HHS News. Baltimore, MD: FDA; February 17, 2000.
103. U.S. Food and Drug Administration. Vaccines: Approved products. Prevnar 13 (pneumococcal 13-valent conjugate vaccine). Rockville, MD: FDA; March 26, 2010.
104. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force. 2nd ed. Baltimore, MD: Williams & Wilkins; 1996.
105. Vlachopoulos CV, Terentes-Printzios DG, Aznaouridis KA, et al. Association between pneumococcal vaccination and cardiovascular outcomes: A systematic review and meta-analysis of cohort studies. Eur J Prev Cardiol. 2015;22(9):1185-1199.
106. Vojtek I, Nordgren M, Hoet B. Impact of pneumococcal conjugate vaccines on otitis media: A review of measurement and interpretation challenges. Int J Pediatr Otorhinolaryngol. 2017;100:174-182.
107. Walters JA, Smith S, Poole P, et al. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010;(11):CD001390.
108. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1:CD001390.
109. Wannarong T, Ekpatanaparnich P, Boonyasiri A, et al. Efficacy of pneumococcal vaccine on otitis media: A systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2023;169(4):765-779.
110. Whiteside J, Grover M, Hitchcock K, Kim R. Clinical inquiries. Should patients receive 23-valent pneumococcal vaccination more than once? J Fam Pract. 2006;55(9):809-812.
111. Whitney CG. Cochlear implants and meningitis in children. Pediatr Infect Dis J. 2004;23(8):767-768.
112. William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: A comprehensive review. Part II: Clinical manifestations, diagnosis, and management. Hematology. 2007;12(2):89-98.
113. Williams RM. Pneumococcal vaccination. Lippincotts Prim Care Pract. 1998;2(6):625-633.
114. Wong WY. Prevention and management of infection in children with sickle cell anaemia. Paediatr Drugs. 2001;3(11):793-801.
115. World Health Organization (WHO). Pneumococcal vaccines. WHO position paper. Wkly Epidemiol Rec. 1999;74(23):177-183.
116. Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc. Prevnar 13 (pneumococcal 13-valen conjugate vaccine (Diphtheria CRM197 protein) suspension for intramuscular injection. Precribing Information. Philadelphia, PA: Wyeth; revised July 2019.
117. Wyeth Pharmaceuticals LLC, a subsidiary of Pfizer Inc. Prevnar 20 (pneumococcal 20-valent Conjugate Vaccine), suspension for intramuscular injection. Prescribing Information. Philadelphia, PA: Wyeth; revised April 2023.
118. Yu J, Li B, Chen X, et al. Comparison of immunogenicity and protection of two pneumococcal protein vaccines based on PsaA and PspA. Infect Immun. 2018;86(6).

Policy History

- Last Review 04/01/2025

  Effective: 07/21/1995

  Next Review: 07/24/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes