AHP & MHA Clinical Spotlight: Vaxneuvance™ (pneumococcal 15-valent conjugate vaccine), Merck & Co.

Overview of Vaxneuvance™

Vaxneuvance™ was FDA-approved via the Priority Review pathway for the prevention of pneumonia and invasive disease from 15 different serotypes of *Streptococcus pneumoniae* (*S. pneumoniae*) in adults 18 years of age and older.[1]

Overview of Pneumococcal Disease

Pneumococcal disease is categorized as invasive (ie, meningitis, bacteremia, bacteremic pneumonia) or non-invasive (ie, non-bacteremic pneumonia, acute otitis media, sinusitis).[2] The symptoms of invasive disease overlap with those of pneumonia from other causes (eg, productive cough, dyspnea, productive cough with rusty sputum, hypoxia, and weakness).[3]

Three-quarters of pneumococcal pneumonia cases are non-bacteremic, and only up to 15% of pneumonia cases in the United States are due to *S. pneumoniae*.[4] However, in cases of invasive pneumococcal disease, *S. pneumoniae* is the pathogen responsible for up to half of cases with known etiology and results in approximately 150,000 hospitalizations annually in the United States.[5] Although there are over 90 serotypes of *S. pneumoniae*, only a few are responsible for most invasive disease.[4,6] *S. pneumoniae* is carried primarily by young children; however, *S. pneumoniae* can be found in the nasopharynx of up to 90% of healthy people.[4] The transmission of this pathogen is through respiratory tract droplets, and its spread is related to crowds, seasons where people are frequently indoors, and the presence of upper respiratory infection.[6]

Patients at greatest risk for pneumococcal disease are the very old and the very young.[3] Other patients at risk include those who are immunocompromised, have pre-existing medical conditions (ie, cardiovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes, cerebrospinal fluid leaks), have cochlear implants, and smoke cigarettes.[7] The mortality risk following hospitalization from community-acquired pneumonia (as opposed to hospital-acquired pneumonia, which is less common) can remain increased for more than ten years.[8]

Bacterial community-acquired pneumonia resulting in hospitalization is most commonly caused by pneumococcal infection (up to 25% of cases in the United States).[7] The mortality rate for patients who require hospitalization for bacteremic pneumococcal pneumonia ranges from 12 to 15% while in the hospital to 35% within 90 days. In comparison, non-invasive (ie, non-bacteremic pneumonia) is associated with a 50% reduction in mortality rates.[7]

Recovery from pneumococcal pneumonia is slow, sometimes taking weeks to months before the patients return to their baseline health status.[7] As a result, community-acquired pneumonia negatively impacts quality of life, even after recovery from illness, particularly in the older population.

In addition to the burden on the quality of life, pneumonia presents an economic burden as it is the eighth-most costly hospitalization, with an estimated total cost of $9.5 million (in 2013).[9] Indirect costs associated with community-acquired pneumonia are also significant and include time off from work and loss of productivity.

Prevention of pneumococcal pneumonia and invasive disease is through standard infection control measures (such as hand washing, surface disinfecting, and containing coughs and sneezes) and also via vaccination. There are two types of pneumococcal vaccines: the pneumococcal polysaccharide vaccine (PPSV23), which contains polysaccharide antigen from 23 serotypes of pneumococcal bacteria, and pneumococcal conjugate vaccines (PCVs), which are conjugated to a nontoxic variant of the diphtheria toxin.

PCVs cover a certain number of *S. pneumoniae* serotypes. PCV-7 became available in 2000, followed by PCV-13 in 2010 (replacing PCV-7), PCV-20 in June 2021, and PCV-15 (Vaxneuvance™) in July 2021.[10] PPSV23 and PCV-13 are approved for use in children and adults; Vaxneuvance™ and PCV-20 are currently FDA-approved for use in adults only as both products are currently under investigation for pediatric use.

Vaxneuvance™: Place in Therapy

Infection with *S. pneumoniae* serotype 3 can result in empyema, bacteremia-induced septic shock, cardiotoxicity, and meningitis.[11] These infections have a fatality rate of 30%–47%, depending on the patient's co-morbidities and age.[11] Serotype 3 is a capsulized pneumococcal strain, making it more virulent and challenging for pneumococcal vaccines to protect against it.[11]

Serotype 3 continues to be responsible for invasive pneumococcal disease despite being covered by PCV-13 and PPSV23.[11] Vaxneuvance™ has been shown to produce superior immune responses compared to PCV-13 against serotype 3.[12] In addition, Vaxneuvance™ includes two serotypes not found in PCV-13 (22F and 33F). The impact of Vaxneuvance's™ enhanced antibody activity against serotype 3 on the overall incidence of serotype 3 disease is unknown, and warrants continued study.

Investigators conducted a study to evaluate the concomitant use of Vaxneuvance™ and a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; QIV).[12] They found that this combination was non-inferior versus using each of these vaccines at different times.

The Center for Disease Control's Advisory Committee on Immunization Practices recently issued its recommendations on the role of Vaxneuvance™ and other pneumococcal vaccines. Note that Vaxneuvance™ is given in addition to PPSV23 to provide broad coverage against nine serotypes not covered by Vaxneuvance™. Table 1 summarizes the recommendations published in *Morbidity and Mortality Weekly Report* on January 28, 2022.

Table 1: Place in Therapy – Pneumococcal Vaccines[13]

Product	ACIP Guideline Recommendations	For use in Children (Y/N)?	*S. pneumoniae* Serotypes covered
PCV20	Adults ≥ 65 years of age who have not been vaccinated with a pneumococcal conjugate vaccine (or with unknown vaccination history): either Vaxneuvance™ or PCV20. (Patients who receive Vaxneuvance™ should then receive a dose of PPSV23, usually ≥ 1 year later) Adults ≥ 19 years of age with risk factors or medical conditions warranting vaccination for pneumococcal disease who have not been vaccinated with a pneumococcal conjugate vaccine (or with unknown vaccination history): either Vaxneuvance™ or PCV20.(Patients who receive Vaxneuvance™ should then receive a dose of PPSV23, usually ≥ 1 year later) Adults with previous PPSV23 only: Adults who have only received PPSV23 may receive a PCV (either PCV20 or Vaxneuvance™) ≥ 1 year after their last PPSV23 dose. When Vaxneuvance™ is used in those with a history of vaccination with PPSV23, it need not be followed by another dose of PPSV23. Adults with previous PCV13: The incremental public health benefits of providing Vaxneuvance™ or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23 series. (For adults who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available.)	No	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F
PPSV23		Yes	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F
Vaxneuvance™ (PCV15)		No	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F
PCV13	Not included in recommendations	No	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

(ACIP: Center for Disease Control's Advisory Committee on Immunization Practices)

Vaxneuvance™: Clinical Studies

Study 1[12]
Researchers enrolled 1,205 adults 50 years of age and older (mean age: 66 years; 57.3% female; 67.75 white) in a double-blind, active comparator-controlled study to assess serotype-specific opsonophagocytic activity (OPA) in pneumococcal vaccine-naïve patients. OPA responses were evaluated for the 15 serotypes covered by Vaxneuvance™ at 30 days post-vaccination. Researchers found that Vaxneuvance™ was non-inferior to PCV13 for the 13 shared serotypes. Furthermore, Vaxneuvance™ induced statistically significant greater OPA geometric mean titers (GMTs) versus PCV13 for shared serotype 3 and for serotypes 22F and 33F (which are unique to Vaxneuvance™). Further study is warranted to determine the clinical efficacy of Vaxneuvance™ versus PCV13.

Study 3[12]
To compare the efficacy of PCV13 versus Vaxneuvance™, investigators conducted a double-blind, active comparator-controlled trial in adults 50 years of age and older. Patients were randomized to receive Vaxneuvance™ (N = 327) or PCV13 (N = 325) followed by PPSV23 a year later. Study results revealed that OPA GMTs values were comparable for patients in both arms of the trial for the 15 serotypes covered by Vaxneuvance™.

The CDC summarized two cost-effective analyses of vaccination with Vaxneuvance™ followed by PPSV23.[13] This analysis also included adding PPSV23 to PCV20. Results of the study revealed that a vaccination series including Vaxneuvance™ followed by PPSV23 resulted in cost savings ranging from $250,000 to $656,000.

Table 1: Vaxneuvance™ (pneumococcal 15-valent conjugate vaccine), Merck & Co.[12]

FDA Approved Indications, Dosage and Administration	Safety Considerations, Storage, Available Forms
Indications: for active immunization in 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 adults ≥ 18 years of age. **Dosage/Administration:** a single 0.5 mL dose given via intramuscular injection. Shake prefilled syringe horizontally immediately before use to obtain an opalescent suspension. Do not use the vaccine if it cannot be resuspended or if there is any particulate matter or discoloration. Special populations: Pregnant women: there are no adequate and well-controlled studies of Vaxneuvance™ in pregnant women. Therefore, data are insufficient to inform vaccine-associated risks in pregnancy. Older adults: clinical trials revealed no clinically meaningful differences in the safety profile or immune responses in older individuals (65 to 74 years and ≥75 years of age) when compared to younger patients. Pediatrics: the safety and effectiveness of Vaxneuvance™ in individuals younger than 18 years of age have not been established. Patients with HIV infection: the effectiveness of Vaxneuvance™ in HIV-infected individuals has not been evaluated.	**Adverse Events:** The most commonly reported solicited adverse reactions: in patients according to age: 18 through 49 years of age: 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%). ≥ 50 years of age: 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%). **Contraindications:** severe allergic reaction (eg, anaphylaxis) to any component of Vaxneuvance™ or diphtheria toxoid. **Drug Interactions:** immunosuppressive therapies may reduce the immune response to this vaccine. **Storage:** Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light. **Available Forms:** sterile suspension of purified capsular polysaccharides from *S. pneumoniae* for injection (0.5 mL dose), supplied as a single-dose prefilled syringe. Each *S. pneumoniae* serotype is grown in media containing yeast extract, dextrose, salts, and soy peptone. The prefilled syringe's tip cap and plunger stopper are not made with natural rubber latex.

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