

PNEUMOVAX® 23 **(PNEUMOCOCCAL VACCINE POLYVALENT)**

DESCRIPTION

PNEUMOVAX® 23 (Pneumococcal Vaccine Polyvalent) is a sterile, liquid vaccine for intramuscular or subcutaneous injection. It consists of a mixture of highly purified capsular polysaccharides from the 23 most prevalent or invasive pneumococcal types of *Streptococcus pneumoniae*, including the six serotypes that most frequently cause invasive drug-resistant pneumococcal infections among children and adults in the United States.¹ (See Table 1.) The 23-valent vaccine accounts for at least 90% of pneumococcal blood isolates and at least 85% of all pneumococcal isolates from sites which are generally sterile as determined by ongoing surveillance of U.S. data.²

PNEUMOVAX 23 is manufactured according to methods developed by the Merck Research Laboratories. Each 0.5 mL dose of vaccine contains 25 µg of each polysaccharide type in isotonic saline solution containing 0.25% phenol as a preservative.

Table 1
23 Pneumococcal Capsular Types Included in PNEUMOVAX 23

Nomenclature	Pneumococcal Types																						
Danish	1	2	3	4	5	6B**	7F	8	9N	9V**	10A	11A	12F	14**	15B	17F	18C	19F**	19A**	20	22F	23F**	33F
** These serotypes most frequently cause drug-resistant pneumococcal infections ¹																							

CLINICAL PHARMACOLOGY

Pneumococcal infection is a leading cause of death throughout the world³ and a major cause of pneumonia, bacteremia, meningitis, and otitis media.

Strains of drug-resistant *S. pneumoniae* have become increasingly common in the United States and in other parts of the world. In some areas as many as 35% of pneumococcal isolates have been reported to be resistant to penicillin. Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs (e.g., erythromycin, trimethoprim-sulfamethoxazole and extended-spectrum cephalosporins), therefore emphasizing the importance of vaccine prophylaxis against pneumococcal disease.

Epidemiology

Pneumococcal infection causes approximately 40,000 deaths annually in the United States.¹

At least 500,000 cases of pneumococcal pneumonia are estimated to occur annually in the United States; *S. pneumoniae* accounts for approximately 25-35% of cases of community-acquired bacterial pneumonia in persons who require hospitalization.¹

Pneumococcal disease accounts for an estimated 50,000 cases of pneumococcal bacteremia annually in the United States. Some studies suggest the overall annual incidence of bacteremia to be approximately 15 to 30 cases/100,000 population with 50 to 83 cases/100,000 for persons 65 years of age and older and 160 cases/100,000 for children less than two years of age.

The incidence of pneumococcal bacteremia is as high as 1% (940 cases/100,000 population) among persons with acquired immunodeficiency syndrome (AIDS).

In the United States, the risk of acquiring bacteremia is lower among whites than among persons in some other racial/ethnic groups (i.e., blacks, Alaskan Natives, and American Indians).

Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteremia is 15-20% among adults⁴, and among elderly patients this rate is approximately 30-40%. An overall case-fatality rate of 36% was documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia.¹

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In the United States, pneumococcal disease accounts for an estimated 3,000 cases of meningitis annually. The estimated overall annual incidence of pneumococcal meningitis is approximately 1 to 2 cases per 100,000 population. The incidence of pneumococcal meningitis is highest among children six to 24 months and persons aged ≥ 65 years; rates for blacks are twice as high as those for whites or Hispanics. Recurrent pneumococcal meningitis may occur in patients who have chronic cerebrospinal fluid leakage resulting from congenital lesions, skull fractures, or neurosurgical procedures.¹

Invasive pneumococcal disease (e.g., bacteremia or meningitis) and pneumonia cause high morbidity and mortality in spite of effective antimicrobial control by antibiotics.⁴ These effects of pneumococcal disease appear due to irreversible physiologic damage caused by the bacteria during the first 5 days following onset of illness,^{5,6} and occur regardless of antimicrobial therapy.^{5,7} Vaccination offers an effective means of further reducing the mortality and morbidity of this disease.

Risk Factors

In addition to the very young and persons 65 years of age or older, patients with certain chronic conditions are at increased risk of developing pneumococcal infection and severe pneumococcal illness.

Patients with chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy), chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease or emphysema), or chronic liver diseases (e.g., cirrhosis), diabetes mellitus, alcoholism or asthma (when it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids) have an increased risk of pneumococcal disease. In adults, this population is generally immunocompetent.¹

Patients at high risk are those who have a decreased responsiveness to polysaccharide antigen or an increased rate of decline in serum antibody concentrations as a result of: immunosuppressive conditions (congenital immunodeficiency, human immunodeficiency virus [HIV] infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, or generalized malignancy); organ or bone marrow transplantation; therapy with alkylating agents, antimetabolites, or systemic corticosteroids; chronic renal failure or nephrotic syndrome.^{1,8}

Patients at the highest risk of pneumococcal infection are those with functional or anatomic asplenia (e.g., sickle cell disease⁹ or splenectomy), because this condition leads to reduced clearance of encapsulated bacteria from the bloodstream. Children who have sickle cell disease or have had a splenectomy are at increased risk for fulminant pneumococcal sepsis associated with high mortality.¹

Immunogenicity

It has been established that the purified pneumococcal capsular polysaccharides induce antibody production and that such antibody is effective in preventing pneumococcal disease.^{6,10} Clinical studies have demonstrated the immunogenicity of each of the 23 capsular types when tested in polyvalent vaccines.

Studies with 12-, 14-, and 23-valent pneumococcal vaccines in children two years of age and older and in adults of all ages showed immunogenic responses.^{10,11-14} Protective capsular type-specific antibody levels generally develop by the third week following vaccination.¹³

Bacterial capsular polysaccharides induce antibodies primarily by T-cell-independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor or inconsistent in children aged < 2 years whose immune systems are immature.¹

Efficacy

The protective efficacy of pneumococcal vaccines containing 6 or 12 capsular polysaccharides was investigated in two controlled studies of young, healthy gold miners in South Africa, in whom there was a high attack rate for pneumococcal pneumonia and bacteremia.¹³ Capsular type-specific attack rates for pneumococcal pneumonia were observed for the period from 2 weeks through about 1 year after vaccination. Protective efficacy was 76% and 92%, respectively, in the two studies for the capsular types represented.

In similar studies carried out by Dr. R. Austrian and associates,¹⁵ using similar pneumococcal vaccines prepared for the National Institute of Allergy and Infectious Diseases, the reduction in pneumonia caused by the capsular types contained in the vaccines was 79%. Reduction in type-specific pneumococcal bacteremia was 82%.

A prospective study in France found pneumococcal vaccine to be 77% effective in reducing the incidence of pneumonia among nursing home residents.¹⁶

In the United States, two postlicensure randomized controlled trials, in the elderly or patients with chronic medical conditions who received a multivalent polysaccharide vaccine, did not support the efficacy of the vaccine for nonbacteremic pneumonia.^{17,18} However, these studies may have lacked sufficient statistical power to detect a difference in the incidence of laboratory-confirmed, nonbacteremic pneumococcal pneumonia between the vaccinated and nonvaccinated study groups.^{1,19}

A meta-analysis of nine randomized controlled trials of pneumococcal vaccine concluded that pneumococcal vaccine is efficacious in reducing the frequency of nonbacteremic pneumococcal pneumonia among adults in low-risk groups but not in high-risk groups.²⁰ These studies may have been limited because of the lack of specific and sensitive diagnostic tests for nonbacteremic pneumococcal pneumonia. The pneumococcal polysaccharide vaccine is not effective for the prevention of common upper respiratory disease in children.¹

More recently, multiple case-control studies have shown pneumococcal vaccine is effective in the prevention of serious pneumococcal disease, with point estimates of efficacy ranging from 56% to 81% in immunocompetent persons.^{1,21-26}

Only one case-control study did not document effectiveness against bacteremic disease possibly due to study limitations, including small sample size and incomplete ascertainment of vaccination status in patients.²⁷ In addition, case-patients and persons who served as controls may not have been comparable regarding the severity of their underlying medical conditions, potentially creating a biased underestimate of vaccine effectiveness.^{1,19}

A serotype prevalence study, based on the Centers for Disease Control pneumococcal surveillance system, demonstrated 57% overall protective effectiveness against invasive infections caused by serotypes included in the vaccine in persons ≥ 6 years of age, 65-84% effectiveness among specific patient groups (e.g., persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia) and 75% effectiveness in immunocompetent persons aged ≥ 65 years of age. Vaccine effectiveness could not be confirmed for certain groups of immunocompromised patients; however, the study could not recruit sufficient numbers of unvaccinated patients from each disease group.

In an earlier study, vaccinated children and young adults aged 2 to 25 years who had sickle cell disease, congenital asplenia, or undergone a splenectomy experienced significantly less bacteremic pneumococcal disease than patients who were not vaccinated.^{1,28}

Duration of Immunity

Following pneumococcal vaccination, serotype-specific antibody levels decline after 5-10 years.¹ A more rapid decline in antibody levels may occur in some groups (e.g., children).¹ Limited published data suggest that antibody levels may decline in the elderly > 60 years of age.^{29,30}

The Advisory Committee on Immunization Practices (ACIP) states that these findings indicate that revaccination may be needed to provide continued protection.¹ (See INDICATIONS AND USAGE, *Revaccination*.)

The results from one epidemiologic study suggest that vaccination may provide protection for at least nine years after receipt of the initial dose.²² Decreasing estimates of effectiveness with increasing interval since vaccination, particularly among the very elderly (persons aged ≥ 85 years) have been reported.²³

INDICATIONS AND USAGE

PNEUMOVAX 23 is indicated for vaccination against pneumococcal disease caused by those pneumococcal types included in the vaccine. Effectiveness of the vaccine in the prevention of pneumococcal pneumonia and pneumococcal bacteremia has been demonstrated in controlled trials in South Africa, France and in case-control studies.

PNEUMOVAX 23 will not prevent disease caused by capsular types of pneumococcus other than those contained in the vaccine.

Vaccination with PNEUMOVAX 23 is recommended for selected individuals as follows:

- routine vaccination for persons 50 years of age or older†

† NOTE: The ACIP recommends routine vaccination for immunocompetent persons 65 years of age and older.

