

# 41 Pneumococcal Disease— Epidemiology and Prevention

**Abstract:** *Streptococcus pneumoniae* is a major cause of morbidity and mortality in very young, high-risk adults and elderly population. It kills almost 1.6 million people annually due to pneumonia, bacteremia and meningitis worldwide (more than any other infective cause). Capsular polysaccharide in the pathogenic *Streptococcus pneumoniae* is responsible for its resistance to phagocytosis by the host macrophages and also for inciting severe inflammatory reaction and disease in the host. Antibodies against the capsular polysaccharide can protect the individual from a particular strain of the *Streptococcus pneumoniae* (there are more than 90 serotypes). A polyvalent vaccine containing 23 different polysaccharide antigens, PPV 23 (23 serotypes most frequently causing disease) can protect the vulnerable population from almost 85% of the pneumococcal disease and is very effective. PPV 23 also contains most of the pneumococcal serotypes which are resistant to number of antibiotics thereby saving the population from the resistant variety of pneumococcal disease. PPV 23 is now included in all the developed countries' adult vaccination programs and is recommended by World Health Organization. There is an urgent need to improve the awareness about pneumococcal disease in India and improve vaccination in the vulnerable population.

*Streptococcus pneumoniae* was recognized as a major cause of pneumonia way back in 1880's. Pasteur in France (who called it Microbe septique mique du salive) and Sternberg in USA (who called it Micrococcus pasteurii) discovered the organism in 1881.

In 1926, the organism was called Diplococcus based on its appearance on gram stain, but later on when it could be cultured in 1974, the name was changed to *Streptococcus pneumoniae* as it grew in chains in the culture media.<sup>1</sup>

Pneumococcal disease is a major cause of death worldwide. It results in almost 1.6 million deaths in a year (700,000 death in persons less than 5 years of age and 900,000 in persons 5 years or more in age). While most of the deaths occur in the developing countries, invasive pneumococcal disease causes high mortality in high risk patients (elderly, with chronic organ failure, diabetics, with immunodeficiency, etc.) even in the developed countries. Approximately 40,000 pneumococcal deaths occur annually in the United States, mostly among the elderly.<sup>1</sup>

## EPIDEMIOLOGY

*Streptococcus pneumoniae* is the causative organism in more than 50% of community acquired pneumonia. Though the most common pneumococcal infections like sinusitis, otitis media and bronchitis are less serious, it is the pneumonia, bacteremia and meningitis which cause most of the mortality. Unfortunately, despite the importance of pneumococcal disease, information on disease burden is scarce in developing countries, particularly in adults. Amazingly pneumococcal disease remains the most preventable cause of death worldwide even more than certain other

vaccine preventable diseases like hepatitis B, measles, meningococcal disease, polio, diphtheria, tetanus, rotavirus and yellow fever.

Almost 20-40% of children and 5-10% adults are colonized with *S. pneumoniae* at some point.<sup>2</sup> The colonization is in the nasopharynx and lasts for 4-6 weeks. During this period, either the individual will develop antibodies against that particular strain and the organism will slowly clear off or the individual can develop infection if the bacteria move to a contiguous area where it is not supposed to be, like eustachian tube, sinuses, lower respiratory tract, and prior to development of antibodies.

The incidence of pneumococcal bacteremic infections is relatively high among infants (due to non development of antibodies) up to 2 years of age and low among teenagers and young adults. Risk rises again with increasing age after 50 years (relative rapid fall in antibody titer). In a South Carolina surveillance study, the incidence of pneumococcal bacteremia among infants, young adult and persons above 70 years of age was 160, 5 and 70 cases per 100,000 populations respectively. For each case of pneumococcal bacteremia (mainly due to pneumonia), there are at least 3-4 non bacteremic pneumonia. Thus there is an average of 20 cases per 100,000 young adults and 280 cases per 100,000 over the age of 70 years annually.

Epidemiological data from India is sparse. In a small study from medical college Shimla, on isolates in community acquired pneumonia, *Strep.pneumonie* was found in almost 35% of patients.<sup>5</sup> In another study published in 1999 from south India, the characteristics of invasive pneumococcal infections was studied in six hospitals in India over 4 years, in patients with suspected pneumonia (3686), pyogenic meningitis (1107), septicemia (257) and localized pus-forming lesions (688). They found 307 isolates of pneumococci, all of them were serotyped. The most frequent in adults were 1, 6, 19, 7, 5, 15, 14, 4, 16, and 18 (in order of frequency). The most common serotypes in children under 5 years were 6, 1, 19, 14, 4, 5, 45, 12, and 7. Serotypes 1 and 5 accounted for 29% of disease.<sup>6</sup> The surveillance is ongoing and further confirmed the same frequency in 681 isolates till 2003.

### **STREPTOCOCCUS PNEUMONIAE: THE BACTERIUM**

*S. pneumoniae* is a gram positive, lancet shaped, facultative anaerobic bacterium.<sup>3,4</sup> These organisms contain a toxic substance known as pneumolysin which causes alpha hemolysis on the blood agar culture (hemoglobin gets degraded into a greenish pigment). These organisms are catalase negative. More than 98% of pneumococcal isolates are susceptible to ethylhydrocupreine (optochin), and virtually all pneumococcal colonies are dissolved by bile salts; these reactions are the basis for laboratory identification.<sup>4</sup>

Some of the pneumococci are encapsulated, with a surface composed of complex polysaccharides. These encapsulated organism are pathogenic, the polysaccharide capsule are antigenic and form the basis for classifying pneumococci by serotype. To date, more than 90 known serotypes have been identified based on their reaction to type specific antisera. Type specific antibodies provide protection against the capsular polysaccharide by interacting with complement to opsonize pneumococci, which helps to facilitate phagocytosis and clearance of the organism mainly by the reticulo-endothelial system.

There are two systems of numbering the serotype, American and the Danish, which is more universally accepted now. In the American system, the serotypes are numbered in the order they are identified. Strains having a lower number are the ones which most frequently cause the human disease. Clearly serotype 1 has to be the commonest organism. In Danish system, serotypes are placed in a group based on their antigenic similarities. For example, Danish group 19 includes types 19F ('first recognized'), 19A, 19B, and 19C, which in the American system would be types 19, 57, 58, and 59, respectively.

## **PATHOGENESIS**

*Streptococcus pneumoniae* attaches to the human nasopharyngeal epithelial cells through an adhesive protein known as pneumococcal surface protein A (PspA).<sup>3,4</sup> The polysaccharide capsule resists clearance from the site, this results into colonization. Infection will result if the organism is carried to the contiguous areas like sinuses or eustachian tubes or lower respiratory tract and the clearance is hindered by mucosal edema due to viral infection or allergy. Once they reach an area where they do not belong, they activate complement by classical and by alternative pathway and stimulate cytokine production resulting in attraction of leukocytes and cause tissue damage. Pneumolysin also plays an important role. The polysaccharide capsule makes it difficult for the organism to be phagocytosed. In the absence of immunity from anticapsular antibody, the phagocytes have limited capabilities and a large inoculum can start the lung infection. Infection of bone, joints, meninges and peritoneum occurs through blood stream spread of bacteria usually from respiratory infections.

Once a pneumococcal infection has been initiated, the absence of a spleen predisposes to fulminant disease. The liver is able to remove opsonized (antibody-coated) pneumococci from the circulation; in the absence of antibody, however, only the slow passage of blood through the splenic sinuses and prolonged contact with reticuloendothelial cells in the cords of Billroth allow time for bacterial clearance. Patients without spleens may die of pneumococcal pneumonia and sepsis at such an early stage of the illness that pulmonary consolidation is not evident on X-ray but rather is found only at autopsy.

If immunoglobulin production is reduced or phagocytosis function is impaired as it happens in immunocompromised host, or in a debilitated, nutritionally poor subject, or in an alcoholic, or patients having chemotherapy, the subject becomes more vulnerable to pneumococcal infection as anticapsular antibody is the best defence mechanism.

## **DRUG RESISTANCE IN *STREPTOCOCCUS PNEUMONIAE***

Up to mid 1970s, the pneumococci were universally susceptible to the all classes of antibiotics.<sup>7</sup> Since 1977, there have been outbreaks of penicillin resistant organism in South Africa. Then it showed resistance to beta-lactams, macrolides, tetracycline and fluoroquinolones. Multicenter surveillance projects have revealed that multidrug-resistant pneumococci are common and increasing. In fact, up to 35% of pneumococcal isolates in some areas are penicillin-resistant. The consequences of pneumococcal antibiotic resistance are manifold, such as treatment failure (worldwide, pneumococcal resistance represents the principal cause of treatment failures for acute respiratory infections and meningitis), the need for expensive alternative antimicrobial agents, prolonged hospitalization, and increased medical costs. Luckily, In India, the resistance is mainly to co-trimoxazole and chloramphenicol and the bacteria still remains largely sensitive to most of the penicillins, though trends of increasing resistance are being seen. PPV 23 (pneumococcal polyvalent vaccine) contains almost 80% of the resistant serotypes.

## **PREVENTION OF PNEUMOCOCCAL DISEASE**

The only way to prevent pneumococcal infections is to vaccinate so that an individual can make antibodies to fight the infection. As there are more than 90 serotypes of pneumococcal strains, ideally the vaccine should have the constituent to make antibodies against all the serotypes to give 100% protection. Antibodies are generated against the polysaccharide capsule of the particular serotype which binds to the capsule and make the bacteria vulnerable for phagocytosis by opsonization.

Pneumococcal polyvalent vaccine was first developed in 1970 and trials were done with vaccines containing 6, 12, or 13 capsular polysaccharides.

Three controlled trials of 6 and 13 valent pneumococcal vaccines were conducted in 12000 healthy, young, adult males mostly from Malawi and Mozambique, where pneumonia is epidemic.<sup>8</sup> Subjects were randomized to receive pneumococcal vaccine containing serotype 1, 3, 4, 7, 8 and 12 in trial 1 and containing serotype 1, 2, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19 and 25 in trials 2 and 3, and group A meningococcal vaccine or saline placebo. The combined protective efficiency of the 6 and 13 valent vaccine against pneumococcal bacteremic pneumonia from all three trials was 83%. The combined efficacy of 13 valent vaccine for trials 2 and 3 was 78.5%.

Couples of trials were done with 6 and 12 valent vaccine in a total of 4,694 South African gold miners in 1970.<sup>9</sup> In one trial, the 6 valent vaccine was administered to 983 subjects, the group A meningococcal vaccine was administered to 1051 subjects and placebo to 985 subjects. In the other trial, the 12 valent pneumococcal vaccine was given to 540 subjects; group A meningococcal vaccine to 585 subject and placebo to 550 subjects. The incidence of pneumococcal pneumonia was significantly reduced by both the 12 valent (protective efficiency 92%) and 6 valent (protective efficiency 76%) versus the combined comparator group.

A meta analysis reviewed the results of 14 prospective, randomized trials in which 6, 12, 13, 14 or 23 valent pneumococcal polysaccharide vaccine was administered to a total of 48,837 immunocompetent adults. In all the trials, the vaccine reduced the incidence of pneumococcal pneumonia by 40 to 71%.<sup>10</sup>

In another study, patients were compared for survival benefit based on their immunization status prior to admission. It was found that survival was significantly improved in adults who received prior pneumococcal vaccine. Also there was a 33% reduction in respiratory failure, 45% reduction in risk of renal failure, 26% reduction in risk of sepsis syndrome and 60% reduction in risk of cardiac arrest during hospitalization. It also decreased the length of stay in the hospital.

23 valent vaccine containing 23 commonest serotype was introduced in 1983. It contained 90% of serotype commonly found and also contained 88% of penicillin resistant serotypes. The serotype contained in the vaccine are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. Once vaccination is given, protective capsular type specific antibody levels generally develop in the 3rd week. The levels would normally decline after 5-10 years. A more rapid decline takes place in children, elderly, patients with nephrotic syndrome etc. PPV-23 vaccine is not recommended for subjects less than 2 yrs of age. 85 % of the isolates found in Indian studies are contained in this vaccine making it suitable for this part of the world.

### **Indication of Polyvalent Pneumococcal Vaccine in Immunocompetent Subjects<sup>11</sup>**

1. Routine vaccination for person > 50 years of age
2. Person aged > 2 years with risks factors (chronic pulmonary disease, chronic heart failure, diabetes mellitus, alcoholism, chronic liver disease, asplenia, CSF leaks, etc.)
3. Person age > 2 years living in special environment or social setting (including Alaskan Natives and certain American Indian population).

### **Indications of Polyvalent Pneumococcal Vaccine in Immunocompromised Subjects**

*In age > 2 years*

- Person with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, any cancer, and nephrotic syndrome
- Person receiving immunosuppressive chemotherapy
- Person with organ on bone marrow transplant.

### **Indications for Revaccination with PPV**

*In Immunocompetent Group:* Revaccination is recommended in:

1. If the patient received initial vaccination in 5 years or more previously and was younger than 50 years of age at that time of vaccination.

2. Revaccination is recommended for person age 2-50 years of age with asplenia (function or anatomical)
  - If the patient is older than 10 years of age, revaccination is done 5 years after the previous dose.
  - If the person is 10 years or younger, a single revaccination is recommended 3 or more years after the previous dose.

*Revaccination in Immunocompromised Group:* In 2 years of age and older including those with

- HIV
- Leukemia, lymphoma, multiple myeloma, any cancer
- CRF, Nephrotic syndrome
- Chemotherapy, patient on long term steroids
- Organ or bone marrow transplants.

If 5 or more years have elapsed since the first dose was administered, single revaccination is recommended.

If the patient is 10 years of age or younger, revaccination should be considered 3 years after the previous dose.

### **VACCINATION IN SPECIAL POPULATION**

Pneumococcal vaccine should be given 2 weeks prior to planned splenectomy, or planned chemotherapy. Vaccination during chemo-therapy or radiation therapy should be avoided, and may be given several months following completion of chemotherapy or radiotherapy for cancer. Persons with HIV infection should be vaccinated as soon as possible after diagnosis.

### **PNEUMOCOCCAL VACCINATION IN CHILDREN BELOW 2 YEARS OF AGE**

Children younger than age 2 years have the highest rates of invasive pneumococcal disease and play an important role in its transmission. In the United States, seven pneumococcal serotypes cause approximately 80% of invasive disease and represent approximately 60% of middle-ear isolates in children younger than age 2 years; the majority of penicillin-resistant strains are confined to these same few serogroups.

PPV 23 is not effective in this age group. A new conjugated pneumococcal vaccine (7 valent) is more immunogenic than the polysaccharide pneumococcal vaccines and is 80-100% effective against vaccine-type invasive disease and 50-60% effective against vaccine-type pneumococcal otitis media. Routine immunization with pneumococcal conjugate vaccines should substantially reduce the morbidity, mortality, and costs associated with pneumococcal disease in children. This vaccine is now included in the routine vaccination schedule of infants below 2 years of age.<sup>12</sup>

### **ADVERSE EFFECT OF VACCINATION**

Adverse effects are few and mainly local reactions like erythema, swelling, induration are seen and are short lived . Fever is seen in some of the patients. The vaccine is given in a dose of 0.5 ml by intra muscular route or subcutaneous.

### **HOW TO IMPROVE VACCINATION IN THE COMMUNITY?**

Despite strong recommendations for the adult pneumococcal vaccination, still there is a very poor response. In the vulnerable segment from age 18 to 65 years in USA, only 19 % are vaccinated till reports of 2002 are available. Among age group of more than 65 years, there was a better response of almost 65% vaccinated by 2003. One of the ways recommended by CDC and other authorities is to have a standing order (Fig. 1) in the hospitals, nursing homes, at physicians' clinics, where every one who needs to be vaccinated are screened by the paramedical staff for the vaccination status and offer vaccination without physician's order if the subject falls

in the designated group who require to be vaccinated.<sup>13,14</sup> Standing order has worked for other vaccination programmes like influenza vaccination and it is believed that it should be effective for pneumococcal also. Also public awareness campaigns need to be there as has happened in vaccination for polio and hepatitis A and B.

## SUMMARY

Pneumococcal disease is the most common preventable cause of mortality among all the infections worldwide. Polyvalent polysaccharide vaccine gives protection from about 85% of the common pneumococcal serotypes found and is strongly recommended in the vulnerable segments by a number of medical societies world over. It not only decreases the morbidity and mortality but also decreases the financial strain on the society as such.

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## MULTIPLE CHOICE QUESTIONS

1. Does polyvalent pneumococcal vaccine (PPV) need to be given to a patient who has had proven pneumococcal pneumonia, as there would be antibody formation from this infection and future protection?
  - A. Yes
  - B. No
  - C. No sure
2. Can pneumococcal vaccine be given at the same time as influenza vaccine?
  - A. No
  - B. Yes, in the same arm
  - C. Yes, in different arm
3. Can a recently diagnosed HIV infected patient be given PPV-23?
  - A. Yes, soon after diagnosis
  - B. Best if CD 4 count is above 500
  - C. Cannot be given. Patient can develop the disease
4. When should be PPV given to a patient who is planned to undergo splenectomy or planned for chemotherapy?
  - A. Vaccination no needed
  - B. Any time before splenectomy
  - C. 2 weeks before splenectomy
5. Does PPV administration need to be repeated if it was given prior to the age of 50 years? What are the guidelines for revaccination?
  - A. PPV 23 is a single dose in a lifetime vaccine
  - B. Yes
  - C. There is no guideline for revaccination

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**1. A 2. C 3. A, B 4. C 5. B**