

# Pneumococcal Vaccines

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## Introduction

*Streptococcus pneumoniae* (pneumococcus) is a major cause of morbidity and mortality all over the world. Pneumococci are usually transmitted by droplet secretions, from patients and healthy carriers to other persons resulting in most occasions in the asymptomatic carriage of the pneumococci. Pneumonia, febrile bacteraemia and meningitis are the most common manifestations of invasive pneumococcal disease, whereas bacterial spread within the respiratory tract may result in non-invasive disease, such as middle-ear infection, sinusitis or recurrent bronchitis. The highest incidence of pneumococcal disease occurs in the first years of life and in the elderly people.

Pneumococcal outer surface consists of a cell wall covered by a polysaccharide capsule, which is considered a principal factor of virulence protecting the pneumococcus from phagocytosis. Capsule polysaccharides are highly heterogeneous and at least, more than 90 different capsular serotypes have been described. These polysaccharides are highly immunogenic and antibodies against them are type-specific. The next layer, the cell wall, consists of polysaccharides, teichoic acid and several cell wall associated surface proteins that are responsible for the intense inflammatory reaction that accompanies pneumococcal infections.

Currently, two types of pneumococcal vaccine against the pneumococcal polysaccharide are licensed in Europe, and include a variable number of capsular serotypes: the older 23-valent Pneumococcal Polysaccharide Vaccine (PPV) and the newer 7-valent Pneumococcal Conjugated Vaccine (PCV). The differences in national pneumococcal policy across Europe ranges from no licensure of any pneumococcal vaccine to the introduction of a universal PCV programme in infancy.

## 23-valent Pneumococcal Polysaccharide Vaccine (PPV23)

The PPV23 provides protection against invasive pneumococcal disease due to 23 serotypes in subjects older than two years. These vaccines contain per dose 25 µg of purified capsular polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) accounting for 85-90% of serious pneumococcal disease. Relatively good antibody responses (60-70%) are elicited in most healthy adults following a single intramuscular or subcutaneous immunisation. The immune response is

however low in children less than two years of age and in immunocompromised individuals (HIV/AIDS). Furthermore, polysaccharide vaccines do not induce immunological memory, which is required for subsequent booster responses. The PPV23 is recommended for healthy people over 65 years of age, particularly those living in institutions. Randomised controlled trials in healthy elderly people in industrialised countries have, however, failed to show a beneficial effect of the vaccine, so that recommendation for its use in the elderly is based on data from observational studies showing a significant protective effect against invasive (bacteraemic) pneumococcal disease, but not pneumonia.

### **7-valent Pneumococcal Conjugated Vaccine (PCV7).**

Over the past 15 years, several pneumococcal conjugate vaccines in which a number of *S. pneumoniae* polysaccharides are covalently coupled to a protein carrier have been developed. The unique PCV licensed to date contains seven capsular polysaccharide antigens from *S. pneumoniae*, each of which is conjugated to an inert but immunogenic variant of diphtheria toxoid diphtheria protein CRM (197).

Conjugate vaccines elicit higher antibody levels and a more efficient immune response in infants and young children than the polysaccharide vaccines, as well as a significant immunological memory resulting in a booster antibody response on subsequent exposure to the antigen. The most prevalent serotypes correlated with invasive diseases and antibiotic resistance in USA and other countries were chosen as vaccine candidates. The currently licensed PCV7 contains polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F with a potential coverage of over 85% of the pneumococcal isolates for the USA, 70-75% for Europe, about 65% for Latin America and approximately 50% for Asia. Moreover, these vaccines suppress nasopharyngeal carriage of the pathogen and reduce bacterial transmission in the community protecting unvaccinated individuals as a result of herd immunity, which adds considerable value to their implementation. PCV7 has been licensed in Europe since 2001 for infants and children between 2 months and 2 years of age. In 2004 this license was extended to include vaccination of children up to 5 years and is currently the only PCV licensed in Europe

Various studies have proved the clinical efficacy of the PPV7 against invasive pneumococcal disease with no apparent difference between a two-dose primary course followed by a booster or a three-dose and booster immunisation regimen. It has also been reported a significant impact of vaccination on pneumonia and otitis media caused by vaccine serotypes. The decrease in cases of vaccine-type otitis media was offset by an increase in those due to non-vaccine-types of *S. pneumoniae* and by *H. influenzae*, a phenomenon referred to as "replacement disease". This phenomenon also has recently been observed for invasive pneumococcal disease, with a substantial increase in non-vaccine types especially serotypes 19A and 15, what is even more worrisome, as these serotypes also carry antibiotic resistance.

### **Other conjugate vaccines**

The currently licensed PPV7 does not contain some of the serotypes that cause severe disease in other countries, notably serotypes 1 and 5. New conjugate vaccines that provide more optimal serotype coverage in these countries are in clinical development, including a 9-valent (PCV9, PCV7 plus serotypes 1 and 5), 10-valent (PCV7 plus serotypes 3, 5, and 7F), 11-valent (PCV11, PCV7 plus serotypes 1, 3, 5, and 7F) and 13-valent vaccine (PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A). One of the PCV9 also has the CRM197 as protein carrier whereas other conjugate vaccines use the *H. influenzae* protein D and the outer membrane protein complex (OMPC) from *N. meningitidis*. The PCV9 has shown efficacy against invasive pneumococcal disease both in HIV-uninfected children and in HIV-infected children. This finding is important since HIV-infected children constitute a group with a 40-fold greater risk of developing invasive pneumococcal disease than HIV-uninfected children. As happened with the PCV7, the PCV9 was associated with an increase in disease caused by non-vaccine serotypes.

The proportion of disease-causing serotypes for PCV11 has been found to be at least 80% in most parts of the world. A PCV11 is undergoing an efficacy trial in the Philippines, but it is not clear at this time whether all these conjugate candidate vaccines will be taken to licensure.

### **Other vaccines**

Newer vaccine approaches are being developed in order to provide protective immunity against a larger number of *S. pneumoniae* serotypes, and to circumvent the complexity of manufacture of conjugate vaccines. Several pneumococcal proteins are at an early clinical stage development, including pneumolysin, pneumococcal surface protein (PspA), pneumococcal surface adhesin (PsaA), neuraminidase, and autolysin. Of them, PspA and pneumolysin have proven protective against invasive infections in animal models, showing complementary protection when used in combination.

### **Suggested reading**

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