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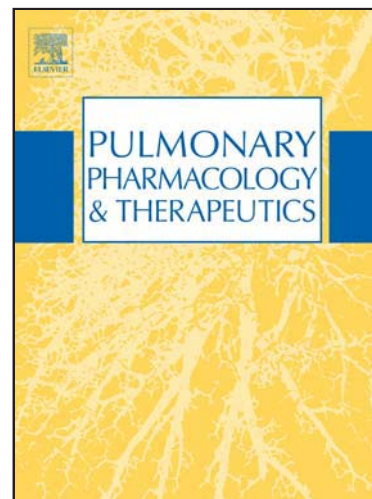
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## **The role of Pneumococcal vaccine: review article**

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**Abstract**

*Streptococcus Pneumoniae* pathologies represent a health problem of primary importance worldwide, in terms of morbidity, mortality, and costs.

*Streptococcus Pneumoniae* is the main aetiological agent of bacterial pneumonia, and is frequently involved in bacterial meningitis, COPD exacerbations and upper airway pathologies.

The high incidence, the level of morbidity and mortality due to pneumococcal pathology despite adequate therapy, and the emergence of antibiotic-resistant strains emphasize the importance of an effective vaccine strategy against this bacterium.

The present review proposes an analysis of current vaccine strategies and their efficacy, with particular stress on their effectiveness in preventing pneumonia.

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**Keywords:** *Streptococcus Pneumoniae*, vaccine, pneumonia, COPD, airway pathologies

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## Introduction

*Streptococcus Pneumoniae* (SP) infections are one of the major causes of morbidity and mortality worldwide; *Pneumococcus* is one of the principal aetiological agents of CAP, bacterial meningitis, otitis media, and chronic obstructive pulmonary disease (COPD) exacerbations. All age ranges are involved, but it is the elderly and children who are particularly at high risk. 100 years ago Sir William Osler already defined pneumonia “a special enemy of old age”, “the natural end of elderly people”. In children aged less than 2, in developed countries, the incidence of the invasive disease has been estimated at 150 cases per year every 100.000 people.

Despite appropriate therapies, mortality due to many SP pathologies remains high, the percentages exceeding 20% in pathologies associated to bacteremia. Every year, in the US alone, more than 40.000 deaths due to SP have been estimated, and this number could increase because of population aging in developed countries and the emergence of antibiotic-resistant strains of SP.

### ***Streptococcus Pneumoniae*: microbiology and clinical aspects**

*Streptococcus Pneumoniae* is a Gram-positive coccus with a diameter of 0.5-1.25 $\mu$ m, a facultative anaerobe arranged in lanceolate-shaped couples and for this reason was originally defined as diplococcus.

The structure of *Pneumococcus* is characterized by a cellular membrane with double lipidic layer, covered by a bacterial wall consisting of peptidoglycan associated with cell wall C polysaccharide; this polysaccharide is identical in all the serotypes, induces non-protective antibodies and was originally used to discover C-reactive protein in human serum. On the outer bacterial surface, *pneumococci* are covered by a polysaccharide capsule.

There are 90 different types of capsular polysaccharide, identifying 90 different serotypes. The polysaccharides in the outer capsule induce protective antibodies and are used in vaccine preparations.

Defence mechanisms against *Streptococcus Pneumoniae* can be schematically divided as immune-mediated and non-immunologic defences. In the first case, the opsonization of the bacterium is determined by complement and type-specific anti-capsular C polysaccharide antibodies, after which a phagocytosis by endothelial network cells

occurs. This takes place especially in the splenic sinusoids and regards both bacteria opsonized by antibodies and complement and non-opsonized bacteria. This accounts for the increased susceptibility to pneumococcal infections in splenectomized subjects or subjects with functional asplenia.

Non-immunologic defences are mainly based on the barrier effect offered by epithelium and mucosa as a whole and by the removal of inhaled agents, including bacteria, induced by cough, pharyngeal reflexes and, above all, ciliary mucus clearance.

Conversely, some risk factors for the development of the pneumococcal disease are represented by immune deficits, both congenital or acquired and pharmacologic. These include HIV, neoplasia, asplenia - including functional asplenia, age extremes, immunodepressive or antiproliferative therapies.

Further risk factors are chronic degenerative organ pathologies, such as diabetes mellitus, chronic kidney insufficiency, nephrotic syndrome, COPD and other pulmonary or cardiovascular pathologies, chronic hepatopathy and all the conditions damaging both the microscopic and macroscopic anatomic integrity of the respiratory tract, with a reduction of the ability to remove secretions and inhaled agents (e.g.: dementia, cigarette smoking).

Moreover, some other socio-economic factors have to be taken into consideration, such as crowding, malnutrition and scarce sanitary conditions, and history of alcoholism and drug addition.

As regards asthma, although some studies have demonstrated an increased risk of pneumococcal pathology in asthmatic patients, there is no clear indication for vaccinating them [1,2].

The transmission of *Pneumococcus* occurs by infected aerosol from man to man; both individuals affected by pneumococcal disease and asymptomatic nasopharyngeal carriers are contagious. In the majority of cases, contagion leads in turn to nasopharyngeal colonization.

Although the carrier status raises adequate antibody response in a fair percentage of cases, the vast majority of pneumococcal infections develop in otherwise healthy nasopharyngeal carriers, with local spread to tissues or invasion of the circulatory torrent and haematogenous spread of the bacterium.

The incidence of pneumococcal disease varies considerably depending on age: it is high in babyhood, it decreases achieving a plateau in young people and in adults, and it increases again as the age grows [3]. Similarly, the percentage of healthy carriers in the

population changes depending on age, and is higher in children, especially infants and toddlers, with percentages ranging from 30% in children aged between 6 and 11 years, to 35-70% in pre-school children.

In adults, the percentage of healthy carriers is lower, as it corresponds to 6%, but increases to 18-30% in adults living in close contact with children [4].

The fact that adults and elderly people in close contact with children have higher percentages of nasopharyngeal colonization by SP and, consequently, greater probabilities to develop the infection, accounts for the beneficial indirect effects of infant vaccination with anti-pneumococcal conjugate vaccine on adult population. Infant vaccination with PCV confers protection both against SP disease and nasopharyngeal colonization; this leads to a reduction in the spread of the bacterium also in non-vaccinated subjects, both children and adults (HERD EFFECT).

*Pneumococcus* is the aetiological agent of several infections, that can be considered invasive when SP is isolated from blood or from other otherwise sterile districts.

Among pneumococcal infections, pneumonia is by far the most frequent. In 75-80% of pneumococcal pneumonias, negative blood cultures are reported using standard isolation methods and are therefore considered as non-invasive diseases. On the contrary, according to the same isolation strategies, SP is isolated from blood cultures in 20-25% of pneumococcal pneumonias and is therefore considered as invasive disease. There is room for future discussion on this definition, when more sensitive molecular techniques should be routinely and successfully applied to the identification of live circulating bacteria. *Pneumococcus* is frequently involved in COPD exacerbations and infections of the middle ear and upper airways with tracheitis, tonsillitis, pharyngitis or sinusitis.

Among pneumococcal invasive infections, about 90% is represented by pneumonia, 5% by meningitis, whereas the remaining 5% is represented by other infections with lower incidence (e.g: isolated Bacteremias, Endocarditis, Septic Arthritis, Pleurisy) [4].

Besides being the most frequent aetiological agent in pneumonia, *Pneumococcus* is also one of the most frequent community acquired agents involved in bacterial meningitis. In the US, every year SP is responsible for 500.000 cases of pneumonia, 50.000 bacteremias, 3.000 meningitis, with a total of 40.000 deaths /year due to SP infection.

As far as community acquired pneumoniae are concerned, SP is responsible for 30-50% hospitalized CAP [5]; among those ones, about 20% are associated with bacteremia.



Mortality due to CAP reaches 5-10% in case of non-invasive disease, and 5-35% in case of invasive disease; but it increases to 10-20% and 18-50% respectively in case of IPD, if patients are more than 65 years old [6,7,8,9,10]. *Pneumococcus* is one of the most frequent pathogens responsible for sinusitis, upper airways infections and COPD exacerbations. Between 30% and 50% of acute otitis media are due to SP infection, with 7 million cases/year in the US [4].

Over the years, many antibiotic resistances of SP have emerged. Those resistances can be added giving rise to multi-drug-resistant bacteria. In Italy, the resistance rate of *Pneumococcus* to penicillin G is about 10-13%: this is a consistent value, but relatively low compared to other European and extra-European countries; penicillin resistance involves mutations of bacterial PBPs that diminish the affinity for the drug.

When using penicillin or amoxicillin/ampicillin intermediate-level resistances (MIC 0,1-2mg/l) can be overcome by increasing drug doses or by using different molecules, such as ceftriaxone, glycopeptides, rifampin or respiratory fluoroquinolones. [11,12]

On the contrary, the high and often combined resistance to tetracycline 22%, cotrimoxazole 26%, and macrolides 35% suggests to avoid where possible the use of these drugs for IPD.[11,12]

### **Pneumococcal infections in COPD**

In patients affected by COPD, there is frequently a bronchial colonization by bacteria that cause infections, exacerbations or pneumonias. Bacterial aetiology of exacerbations varies according to the severity of the underlying disease: *Streptococcus Pneumoniae*, *Moraxella Catarrhalis* and *Haemophilus Influenzae* are responsible for the majority of exacerbations, from slight to severe functional impairments; whereas *Enterobacteriaceae*, *Staphylococcus Aureus* and *Pseudomonas Aeruginosa* are typically involved in exacerbations in patients with more severe functional impairment [13].

According to Ball, *Streptococcus Pneumoniae* is responsible for 15-25% of COPD exacerbations [14,15].

Several evidences have demonstrated that airway colonization with *Streptococcus Pneumoniae* augments the risk of a first COPD exacerbation, namely if it is present as monoculture [16]. A significant increase in exacerbations when *Streptococcus Pneumoniae* is isolated has been confirmed by Sethi et al [17]. Moreover, the study by Bogaert et al. has highlighted that 70% of pneumococcal serotypes isolated in the

sputum of patients with AECOPD were included in the 23-valent vaccine [16]. This aspect further underlines the role of antipneumococcal vaccination in patients affected by COPD, since COPD exacerbations are a very important element in the natural history of the disease: apart from greatly affect mortality, morbidity, costs and quality of life, they also contribute to determining the progressive clinical and functional worsening which is characteristic of this pathology.

### **Antipneumococcal vaccination**

Over the years, two kinds of vaccine have been developed: the 23-valent pneumococcal polysaccharide vaccine (PPV) and the heptavalent pneumococcal conjugate vaccine (PCV) [18]. Both of them exploit the polysaccharide antigens of the pneumococcal capsule and their ability to induce an antibody response by producing specific protective immunoglobulins.

The 23-valent vaccine (PPV) includes 25µg of all the 23 capsular polysaccharides isolated from 23 different pneumococcal strains, purified and treated with phenol. Since it is made up by polysaccharide and non-protein antigens, the PPV induces an antibody response independent from T lymphocytes; for this reason, it has a reduced immunogenicity compared to a hypothetical protein vaccine and it does not produce any immunological memory, therefore lacking of booster effect when administrating other doses after the first one.

The PPV is scarcely immunogenic in children below 2 years of age because of the immaturity of their immune system; for children in this age bracket, the conjugate polysaccharide vaccine is recommended. The conjugate vaccine employs a protein component as adjuvant, allowing to recruit T lymphocytes in the antibody response; in this way, its immunogenicity is increased, thus permitting to obtain immunological responses also in unweaned babies. Moreover, T-dependent response allows to obtain immunological memory.

The 23-valent vaccine includes serotypes 1,2, 3,4,5,6B, 7F,8,9N, 9V,10A,11A, 12F, 14, 15B, 17F, 18C, 19A,19F,20,22F,23F,33F; some of these serotypes have a fair cross-reactivity with serotypes which are not contained in the vaccine (namely 6B,6A,15B,15A), providing potential coverage of more than 23 serotypes. The choice

of serotypes for inclusion in the vaccine was made so as to comprise the main serotypes that have developed antibiotic resistances and the most virulent serotypes, responsible for invasive infections; about 90% of the invasive pneumococcal infections is caused by vaccine serotypes. Finally, serotype 5 was included because it is extremely frequent in Africa [4,19].

The PPV has a good immunogenicity, with a percentage of antibody response of about 75-85% in adult healthy subjects. Responses equal to or slightly inferior to controls are reported in elderly, immunodepressed nephropathics, COPD, splenectomized subjects, and in those affected by chronic organ pathologies [4,19].

The antibody response after a single dose of PPV begins 7-10 days after vaccination; IgM are the first ones to appear but they can be measured only for few months. IgG are characterised by slow growth, with a concentration peak even after 70-100 days, and are long lasting, thus providing long-term immunity.

IgA response is observed after PPV vaccine, although it may be variable and transitory. Caution in evaluating the antibody response to vaccine is needed, as it is necessary to consider that this is a 23-valent vaccine and, therefore, there are different antibody responses against different antigens. In addition there is not a univocal correlation between the antibody level and the protection grade, and it is not possible to establish for certain the antibody protection level, which would be probably different for each of the 23 serotypes.

Qualitative measures of antibody activity (OPA: opsonophagocytic activity test), that better correlate with the protection level, are not used on a large scale [4].

Reduced antibody response to vaccination can occur in several situations. Patients infected by HIV have a weak response during the advanced stages of the disease. For this reason it is recommendable to perform the vaccination early, as the pneumococcal disease is a common infection in HIV-1 infected patients. In splenectomized subjects, a reduced immunogenicity of the vaccine is observed: this is why vaccination before splenectomy is recommended. Should this not be possible, vaccination is however indicated, but in this case it is recommendable to delay the vaccination a few weeks after the operation. Moreover, in subjects affected by neoplasia, in transplanted patients, and in all those who receive immunodepressive therapies, better responses are observed if the vaccination is performed before radio-chemotherapy or immunodepressive therapy, than after them.

As far as steroid treatment is concerned, some studies which involved patients affected by COPD undergoing systemic steroid therapy, nephrotic syndrome and asthma have underlined that such therapy does not influence the response to the PPV [20,21,22].

With respect to immunogenicity and duration of protection, a clinical evaluation of the duration of antibody coverage is not at hand because of its considerable variability. In healthy adults, the antibody level remains high for more than 5 years, and sometimes even for 10 years. A definitely lower duration, of three years or less, can be pointed out in elderly, immunodepressed, splenectomised and nephropathic patients [4]. In the light of the above discussion, vaccination is recommended in all subjects at risk. As patients at risk may remain so over considerable spans of years, it may be necessary to provide revaccination after several years. The term revaccination and not booster is used because the PPV does not involve T lymphocytes in the immunologic response and, therefore, it does not determine any immunologic memory. The proportion of the responses to revaccination is similar to that of primary vaccination; a good response to primary vaccination is a positive predictive factor for good response to revaccination and vice versa.

After the first revaccination, the antibody level rises again, but generally less than after the primary vaccination. Nowadays, there are not definite data about the effective duration of the antibody effect after revaccination, and there are no controlled studies on the effect or efficacy beyond the second revaccination.

Revaccination is well tolerated, although adverse reactions are more frequent and severe, especially local reactions. The risk of side effects after revaccination correlates with pre-vaccination antibody levels; for this reason it is not recommendable to administer further doses of the vaccine before three years from primary vaccination have passed and it is advisable to possibly wait beyond 5 years. Also in this area, the lack of controlled studies limits the value of any clinical evaluation [4].

When assessing the effects of the antipneumococcal vaccination on the population, it is necessary to make a separate evaluation of its efficacy to induce adequate antibody response and its capacity to prevent the pneumococcal disease.

As regards the efficacy of the 23-valent antipneumococcal vaccine, it is possible to express a positive judgment on the basis of its good immunogenicity (with antibody response in 75-85% of vaccinated people), a quite durable response also in elderly people, even if it is very variable, from less than 3 years to more than 8, and the quite

good response to revaccination, even if data are few, especially on the responses to repeated revaccinations.

On the contrary, the assessment of PPV vaccination efficacy in preventing the pneumococcal disease is a still open problem; in particular, a separate evaluation should be made of the efficacy of the vaccination against IPD invasive disease and against non-invasive disease.

Although the first studies in the 70s pointed out the ability of the polysaccharide vaccination to protect both from invasive pneumococcal pneumonia and from non-invasive disease, successive studies did not unanimously agree on those data: in several studies the positive data about protection against invasive disease were confirmed, whereas many doubts were raised about protection against pneumonia not associated with bacteremia, especially when analysing the elderly population separately [4, 23, 24]. According to a meta-analysis published by Cornu and co-workers, the efficacy of the polysaccharide vaccine against invasive disease is confirmed to be superior to 70%, whereas protection against non-invasive pneumococcal pneumonia is about 40% [25] (Table 4).

Data emerging from another meta-analysis performed by Melegaro and co-workers on subjects aged more than 65 confirmed that the efficacy of PPV against invasive disease is about 65%; nevertheless, the efficacy decreases to 20% in people aged more than 65 and at high risk. The efficacy of vaccination against non-invasive pneumonia was about 16% in healthy subjects and it was 0% in people aged more than 65 and at high risk [26].

More optimistic results were obtained in a study performed by Vila-Còrcoles and co-workers. Although confirming the inefficacy of vaccination in preventing pneumococcal pneumonia in elderly subjects, it pointed out a considerable reduction in risk of death by pneumonia in the same subjects. This is probably due to the efficacy of vaccination in preventing bacteremia, that is well known to have a definitely more severe prognosis *quoad vitam* compared to non-invasive pneumonia [27].

In Italy, the PPV antipneumococcal vaccination is indicated and offered free of charge to subjects affected by chronic degenerative organ pathologies, such as diabetes mellitus, chronic kidney insufficiency, nephrotic syndrome, advanced chronic hepatopathy, chronic pulmonary or cardiovascular pathologies, subjects affected by immunodepressive pathologies, splenectomized subjects or with functional asplenia,

institutionalized subjects or aged more than 65. In subjects at high risk revaccination is recommended and offered free of charge every 5 years.

### **Polysaccharide conjugate vaccine and HERD effect**

The heptavalent conjugate vaccine, as it was said before, was studied for children aged less than two, who do not respond to simple polysaccharide vaccine because of the immaturity of their immune system. In this vaccine, purified polysaccharides are conjugated with a protein component of the diphtheric toxoid. The conjugation with protein antigen involves T lymphocytes in the immune response, providing a greater immunogenicity and allowing the establishment of immunologic memory.

In this vaccine, serotypes 4,6B,9V,14,18C,19F,23F are present. They represent the most frequently antibiotic resistant serotypes and the most frequently involved in invasive infections.

The PCV has a good immunogenicity, with antibody response in 60-100% of vaccinated people after a cycle of three doses; it produces immunologic memory, as testified by the booster effect in successive doses after the first vaccine cycle (III doses) in almost all the subjects.

The polysaccharide conjugate vaccine provide an optimal level of protection against invasive disease, with percentages of efficacy of about 90%; however, as well as the 23-valent vaccine, it has a lower efficacy, with percentages ranging from 20% to 90%, against non-invasive pneumonia [28].

The PCV causes greater Ig-A response, compared to PPV; this contributes to provide some efficacy against acute otitis media. This is not a minor aspect, since this pathology has a very high incidence during the first years of life and it has a strong impact in terms of infantile mobility and costs; but especially it causes a reduction in nasopharyngeal carriage of vaccinated serotypes. This is confirmed by several surveys and by a recent study underlining the decline in pneumonia admissions after routine childhood immunization in US population [29].

As earlier said, the reduction of the carrier state in children vaccinated with PCV, together with the inclusion of serotypes that are most frequently involved in invasive disease and in antibiotic resistance, lead to indirect consequences on the whole population that are defined “herd effect”.

This is represented by i) a reduction in the nasopharyngeal colonization rate (and therefore in the pathology) due to vaccine serotypes also in non-vaccinated children and adults; ii) a reduction in the circulation of antibiotic resistant serotypes, that are covered by the vaccine, even in non-vaccinated subjects, with possible gradual increase due to “substitution” of pathology by non-vaccine serotypes [30].

These aspects have been confirmed in a study by Kyaw and collaborators who observed a vast population in the US during the years following the introduction of infantile PCV vaccination ('99-'04). Data from this study show that in those years there has been a reduction of 81% in the incidence of invasive pneumococcal disease caused by penicillin-resistant bacteria in children aged less two, both vaccinated and non-vaccinated.

Kyaw et al. showed the effect of a pneumococcal conjugate vaccine on invasive disease caused by resistant strains. The rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older people after the introduction of the conjugate vaccine and there was an increase in infections caused by serotypes not included in the vaccine [31].

Moreover, this study pointed out that there was a consistent increase in the general population in the incidence of IPD due to penicillin-resistant strains not covered by the heptavalent vaccine (+195%). Most resistant infections from serotype not included in the vaccine were caused by serotypes 6A and 19A; despite of this, considering both vaccine serotypes and serotypes not included in the vaccine, the overall result is a decrease of 57% in the incidence of IPD by penicillin-resistant bacillus (31).

Recent studies have shown an increasing carriage of non-PCV7 serotypes not only in children but also in adult patients and an increasing penicillin-nonsusceptible disease caused by non-PVC7 serotypes [31, 32, 33]. In the U.S. the annual incidence of disease due to non-vaccine serotypes increased from an average of 16.3 cases/100,000 population during prevaccine years (1998-1999) to 19.9 cases/100,000 population in 2004 for children aged <5 years ( $P=.01$ ) and from 27.0 cases/100,000 population during prevaccine years to 29.8 cases/100,000 population in 2004 for adults aged  $\geq 65$  years. Significant increases in the incidences of disease due to serotypes 3, 15, 19A, 22F, and 33F were observed among children during this period ( $P<.05$  for each serotype); serotype 19A has become the predominant cause of invasive disease in children. The incidence of disease due to these serotypes also increased among elderly

persons [33, 34]. Furthermore, a significant increase in antibiotic-resistant isolates belonging to non-vaccine serotypes among children has been noticed [35].

The emergence of replacement disease with non-vaccine serotypes causes great interest in expanding the serotype coverage of conjugate vaccines: 10- and 13-valent conjugate vaccines are being developed [36, 37].

### **Antipneumococcal vaccination in COPD**

The aggregate effectiveness of the pneumococcal vaccine in preventing hospitalisation for IPD has been proved to be around 50-70% [38, 39]. Several trials have given evidence that pneumococcal vaccination to prevent invasive pneumococcal disease in elderly adults is very cost-effective, and this accounts for the wider use of the vaccine in Western Europe [40]. The initial studies of the cost-effectiveness of the pneumococcal vaccination for preventing pneumococcal pneumonia were not persuasive, since no evidence was found of its efficacy [40]. Nevertheless, a study performed in the USA involving patients aged 65 and more proved that the pneumococcal vaccination would be cost-saving if it only prevented hospitalisation for pneumococcal bacteremia [41]. The pneumococcal vaccination of elderly people to prevent IPD has been confirmed to be a cost-effective intervention in studies from the Netherlands [42], France [43], England and Wales [26], Canada [44] and USA [41]. A more recent report from the USA affirms that also extending the pneumococcal vaccination to people aged  $\geq 50$  for preventing IPD alone would be cost-effective [45].

As previously stated, after PPV vaccination in patients affected by COPD, an antibody response is observed which is substantially superimposable to healthy controls. In the same way, the duration of antibody coverage is similar to controls of the same age.

In these patients systemic steroid therapy frequently in progress does not seem to influence neither the vaccine immunogenicity nor the clinic response to vaccination [20].

Encouraging results regarding the efficacy of this vaccine emerged from a recent study conducted by Alfageme et al. on patients affected by COPD and by radiologically confirmed CAP. In this study, the level of protection against CAP turned out to be inversely proportional to patients' age, the efficacy reaching 76% in patients aged less than 65. More interesting, the level of protection was higher in patients with severe functional impairment, especially if young. Data from this study attribute a level of



protection of PPV against CAP of 48% in COPD patients of all age ranges with FEV1 lower than 40%, which reaches 91% in patients aged less than 65 with the same functional impairment [46].

These data have been reported in the last edition of GOLD guidelines, where, besides flu vaccine for all COPD patients, PPV vaccine is recommended in all patients aged more than 65 and in patients of all age ranges with FEV1 lower than 40% [47, 48, 49] (Table 2).

### **Practical observations**

The vaccine must be preserved in the refrigerator at controlled temperature, in order to avoid freezing and maintaining the cold chain. Before performing the vaccination, it is necessary to make a correct vaccination anamnesis, namely to assess reactions to previous vaccinations and hypersensitivity to active principles or excipients contraindicating the vaccination; however, it is necessary to have drugs at hand in the event of severe allergic reaction. In case of feverish diseases or acute infection, it is recommendable to delay the vaccination. As regards the antipneumococcal vaccination during pregnancy, there are no reasons to think that this could cause undesirable effects on foetus, and no negative effects on infants by mothers inadvertently vaccinated during pregnancy were reported; on the contrary, there could be theoretical advantages in vaccinating during the third term of pregnancy, since this could favour the transfer of specific IgG through placenta and increase antipneumococcal IgA in mother's milk, providing protection to the unborn child in the first months. Nevertheless, it is not advisable to use the PPV during pregnancy and lactation because supporting data and appropriate studies are missing. Both the polysaccharide vaccine PPV and PCV must be administered through deep intramuscular injection (deltoid in adults, femoral quadriceps if < 1 year); if intramuscular injection is contraindicated, the vaccine can be injected subcutaneously. Subcutaneous administration of PPV does not influence the vaccine immunogenicity but increases the risk for local adverse reactions [50].

Some studies have been performed on the administration of the 23-valent vaccine by inhalation [51, 52]. This kind of administration was proven to be safe and induced satisfactory antibody response both in healthy subjects and patients affected by COPD.

It is possible to administer PPV and PCV at the same time of other vaccines, but in another site.

In case of multiple injection, it is important to mark the injection site of the different vaccines, to correctly ascribe any local adverse reaction.

The PPV and flu vaccine have similar indications, and in subjects at risk it is recommendable to perform both the antipneumococcal and flu vaccinations. Several studies point out that the two vaccinations have an additive effect on morbidity and mortality due to pulmonary pathology. [53]

It is possible to co-administer the two vaccines, in two different sites. Coadministration does not alter the reciprocal antibody responses nor increases side effects, reduces costs and allows the recruitment of a greater number of subjects at risk [4].

Among the possible adverse reactions due to vaccination there are local reactions in the injection site, which are quite common (30-50%) especially in young subjects with erythema, hardening and pain in the injection site, associated with functional impotence. These reactions, in general slight, naturally withdraw in 1-3 days. Functional rest, application of ice and use of NSAID are recommendable.

Systemic slight reactions can occur in 2-10% of vaccinated subjects, with fever, general indisposition, myalgias; spontaneous resolution generally occurs in 1-3 days.

Finally, high fever, headache, arthralgia, asthenia, lymphadenopathy, anaphylactoid reactions, urticaria, rash and severe reactions, such as anaphylactic reactions, S. Guillain Barré, etc, are rarely observed [4].

### **Future perspectives**

Some studies have been performed evaluating the administration of PCV alone or associated with PPV in adult subjects, with the aim of exploiting the greater immunogenicity and the ability to induce immunologic memory. The results were not positive in terms of antibody response and appearance of booster effect. [54, 55]

Nevertheless, it has to be considered that the PCV vaccine contains an antigen dosage calibrated for children not for adults, and that even in children repeated administrations are needed to provide immunologic memory. Further controlled strategic studies are needed on this point.

A recent study comparing the immunogenicity of PVC7 at varying doses to PPSV23 in healthy patients who had been previously vaccinated with PPSV23, has demonstrated that the administration of the conjugate vaccine to adult patients is safe [56, 57, 58]. It has also been proven that the PCV7 vaccine induces higher antibody titres and opsonizing response to the included serotypes in comparison to PPSV23. Moreover, a

dose-response effect with greater immunogenicity has been shown after administration of a 0.1 mL and 2.0 mL PCV7 dose than with the paediatric dose of 0.5 mL. However, these vaccines did not induce any significant antibody response upon re-challenge with PPSV one year after the first vaccination.

These studies collide with the higher costs of a hypothetical vaccine calendar combined with PPV and PCV and a greater number of administrations, and with the fact that the conjugate pneumococcal vaccine offers coverage to a more limited number of serotypes compared to 23-valent PPV [19].

Conjugate vaccines are being studied that will include a greater number of serotypes, chosen among the most virulent, more frequently drug-resistant and among those which replaced the serotypes covered by the 7-valent vaccine. Namely, the 11-valent vaccine is being studied together with the 13-valent vaccine, that covers 6A and 19A serotypes, responsible for an increasing number of invasive infections after the introduction of the 7-valent vaccine. [59, 60, 34]

Whether partial PCV7 vaccine coverage (max 50%) may result in the observed decrease in antibiotic-resistant strains an increase in invasive pneumococcal disease observed in Spain is still to be confirmed [61]. The interaction of the extremely high prevalence of penicilli-resistant pneumococci in Spain [11] with the low PCV coverage and low proportion of PCV7-included circulating strains reported in this study could be responsible for the observed paradoxical effect.

Some protein vaccines are being studied, which are composed of non-capsular pneumococcal virulence factors, such as Pneumolisin, PspA, PsaA, PspC, PhtB, PhtE.

The potential advantage of this kind of vaccine is that they have epitopes common to all the serotypes, instead of the capsular polysaccharide antigens contained in PPV and PCV. Moreover, the presence of protein epitomes would induce T-dependent response, with greater immunogenicity and induction of immunologic memory [62]. An additional strategy that needs to be addressed is represented by the induction of antibodies directed against virulence factors and damage mediators that can, by interfering with them, modify the clinical expressivity of the disease, even irrespective of proper protective effect [19, 63].

Finally, a critical appraisal of the existing published experience on PCV7 is needed to address future questions that still afflict everyday clinical practice. When evaluating the results obtained in Spain and the USA, discrepancies are evident [31, 33, 61]. Based on available evidences, the usefulness of a PCV depends on the extension of coverage, on

the inclusion of locally circulating serotypes and on the proportion of antibiotic-resistant pneumococcal strains. Inhomogeneous pneumococcal strain circulation is evident when comparing results of studies in the US and Spain where strain coverage by the PCV7 was reported to be >80% and 60% respectively [33, 61]. The appearance of increasing proportions of invasive pneumococcal disease due to serotype 19A [34, 59, 60] are in line with this concept and also point out the need to either expand the number of antigens included in the vaccine tools (Table 1), or to devise modular production and distribution based on local needs of macro areas. The lower circulation of antibiotic-resistant pneumococci in some European countries [11] as for penicillin resistance in Northern Europe compared with Southern Europe (25% vs.6%) [64] should also induce to expect lower benefits of the PCV vaccination in terms of protection from antibiotic resistant strains in these areas, while maximum benefits could be observed in Africa and the Far East, where higher rates of resistant strains have been reported [64](Table 3).

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Table 1: serotypes included in the vaccines

23valent PPV	1	2	3	4	5	6B			7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19A	19F	20	22F	23F	33F
7valent PCV				4		6B						9V				14			18C		19F			23F	
11valent PCV	1		3	4	5	6B		7C				9V				14			18C		19F			23F	
13valent PCV	1		3	4	5	6B	6A		7F			9V				14			18C	19A	19F			23F	

Table 2: PPV vaccination guidelines

Vaccination recommended in subjects aged $\geq 65$ years, and in subjects at risk of pneumococcal pathology aged $>2$ years*	Evidence level II: moderate	According to IDSA/ATS Guidelines 2007	Revaccination recommended after 5 years in adults aged $\geq 65$ years who have received the first dose before 65 years and in subjects with asplenia or immunodepression
Vaccination recommended in subjects aged $\geq 65$ years, and in subjects at risk of pneumococcal pathology aged $>2$ years *	Degree of recommendation B4	According to ERS Guidelines 2005	Revaccination can be considered in elderly people, 5-10 years after the first vaccination (B3)

\* subjects affected by chronic cardiovascular, pulmonary, hepatic, or kidney pathologies, diabetes mellitus, damaged immune system due to pathology of pharmacology, anatomical or functional asplenia, dementia, pathologies with chronic cerebrospinal fluid loss, people living in nursing homes

Table 3: Future prospects and requirements for pneumococcal prophylaxis

New vaccination guidelines	PPV vaccination of healthy smokers (suggested by Pneumonia Guideline Committee) Particular stress on the importance of stop smoking in smokers hospitalized for CAP recommended by IDSA/ATS '07, evidence level III)
Vaccinal coverage implementation	Realization of widespread vaccine campaigns Evaluation of vaccinal status when entering the hospital and vaccination of subjects at risk before discharging or during post-hospitalization (recommended by IDSA/ATS '07, evidence level III)
Vaccine modifications	Inclusion of serotype 19 A in the conjugate vaccine because frequently pharmaco-resistant (will be only available in the 13-valent PCV)
Expanded trials	Ad hoc trials to verify usefulness and advantages of protection in elderly and at risk populations with new PCV vaccines or PCV-PPV combinations

Accepted manuscript

Table 4 – Efficacy of Antipneumococcal vaccine in pneumonia prevention.

Disease	Vaccine	Trial	Author	Year	Journal	Patients	Efficacy
Pneumococcal pneumonia in general population	PPV	Meta-analysis	Cornu et al	2001	<i>Vaccine</i>	48000	
Invasive							71%
Non-invasive							40%
Pneumococcal pneumonia in >65 years	PPV	Meta-analysis	Melegaro et al	2004	<i>European Journal of Epidemiology</i>		
Invasive							65%
Non-invasive							16%
Pneumonia in COPD (general population)	23-valent PPV	Randomized controlled trial	Alfageme et al	2006	<i>Thorax</i>	600	24%
Pneumonia in COPD in <65 years							76%
Pneumonia in COPD with FEV <sub>1</sub> <40%							48%
Pneumonia in COPD with FEV <sub>1</sub> <40% and age <65 years							91%

Accepted