

Current Perspectives for Antipneumococcal Vaccination in Patients with Chronic Obstructive Pulmonary Disease

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SUMMARY

Streptococcus pneumoniae, the most common cause of community-acquired pneumonia, remains a major cause of morbidity and mortality worldwide. The presence of Chronic Obstructive Pulmonary Disease (**COPD**) is a major risk factor for pneumonia, and smoking (the most common cause of COPD) is also an important risk factor to suffer invasive pneumococcal disease.

This article describes immunological characteristics, advantages and shortcomings, clinical efficacy and cost-effectiveness for distinct anti pneumococcal vaccination strategies for COPD patients.

To date, there are three established approaches to anti-pneumococcal vaccination: capsular Polysaccharide Pneumococcal Vaccines (**PPV**), protein-polysaccharide conjugate Pneumococcal

Vaccines (**PCV**) and experimental Protein-Based Pneumococcal Vaccines (**PbPV**). At present, two vaccines are available for using in COPD patients in clinical practice: the “classical” 23-valent PPV and the “new” 13-valent PCV.

The main advantage for the PCV13 is the fact that it has better immunogenicity than PPV23, but a major shortcoming is the fact that it is directed against strains that are likely to be greatly reduced in the population since its introduction in childhood immunization. The main shortcoming for the PPV23 is its poor immunogenicity than PCV13 but, as major advantage, it may provide protection against ten additional serotypes.

At present, the following recommendations can be made for COPD patients: a) those COPD patients with immune compromising conditions (i.e., steroids or immune modulating therapy, current sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, human immunodeficiency virus infection/acquired immunodeficiency syndrome, nephrotic syndrome, and hematologic or solid malignancies) should receive dual vaccination with PCV13 and PPV23 (preferably PCV13 followed by PPV23 eight weeks later or, alternatively, PPV23 followed by PCV13 at least one year later); b) for those COPD patients without the above mentioned conditions, according most committees on immunization practices, dual vaccination is unnecessary and they should receive only a dose of PPV23 (with a second dose for revaccination at 5-10 years after receipt prime PPV23 in those COPD patients aged less than 65 years). Some clinical guidelines recommend also PCV13 in COPD patients without immune compromising conditions, but this strategy has not demonstrated its cost-effectiveness.

Abbreviations: ACIP-Advisory Committee on Immunization Practices; CAP-Community Acquired Pneumonia; CDC-Centers for Disease Control and Prevention; CI-Confidence Interval; COPD-Chronic Obstructive Pulmonary Disease; EMA: European Medicines Agency; FDA-Food and Drug Administration; OR-Odds Ratio; PPV-Pneumococcal Polysaccharide Vaccine; PCV-Pneumococcal Conjugate Vaccine; PbPV-Protein Based Pneumococcal Vaccine; RCT-Randomized Controlled Trial; IPD-Invasive Pneumococcal Disease

Keywords: Chronic Obstructive Pulmonary Disease; Conjugate Pneumococcal Vaccine; Effectiveness; Efficacy; Pneumococcal Vaccination; Polysaccharide Pneumococcal Vaccine; Streptococcus Pneumoniae

INTRODUCTION

Streptococcus Pneumoniae, the most common cause of Community-Acquired Pneumonia (**CAP**), remains a major cause of morbidity and mortality worldwide. Despite appropriate antibiotic therapy and intensive care treatment, mortality rates due to pneumococcal infections remain considerable, especially in elderly and high-risk individuals such as patients with chronic respiratory or pulmonary disease [1,2].

The main reservoir of pneumococci is the nasopharynx, and the possible outcomes after colonization are clearance by the organism, asymptomatic persistence of infection (carrier state), or progression to disease. Disease presentation depends on whether the bacteria spreads to adjacent mucosal tissues causing mucosal infections (otitis, sinusitis, bronchitis and nonbacteraemic pneumonias) or whether it invades the bloodstream, or other sterile sites, resulting in Invasive Pneumococcal Disease (**IPD**), principally bacteraemic pneumonia, meningitis and sepsis. The outcome is a complex process that depends on interactions between factors related to the host, therapy and microorganism [3,4]. Figure 1 illustrates the overlap between overall community-acquired pneumonia, pneumococcal pneumonia and IPD.

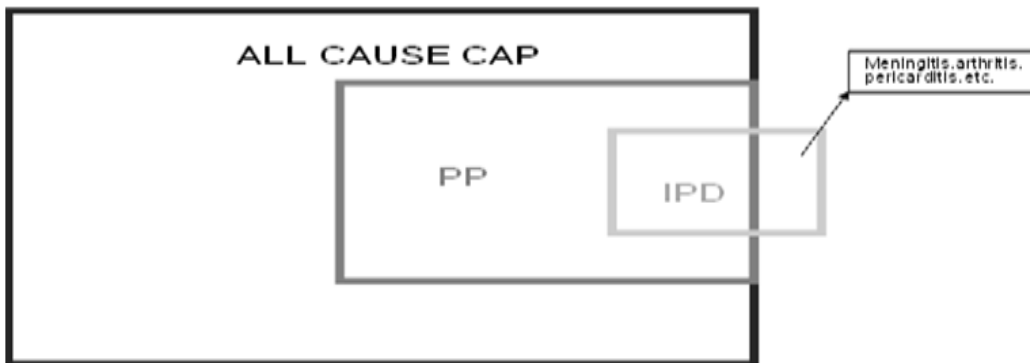


Figure 1: Overlap between overall community-acquired pneumonia, Pneumococcal Pneumonia (**PP**) and IPD.

The reported incidences of IPD have widely varied in different studies. These differences probably reflect different rates of obtaining blood cultures from patients with pneumonia. The incidence of bacteremic pneumococcal pneumonia ranged from 9 to 18 cases per 100,000 adults-years in a multicentre study carried out in five countries [5]. The true incidence of nonbacteremic pneumococcal pneumonia is unknown, but it is probably 3-4 fold higher considering that it has been estimated that 80% of all pneumococcal pneumonias happen without bacteremia [6,7].

Chronic Obstructive Pulmonary Disease (**COPD**) is a major risk factor for CAP, and smoking (the most common cause of COPD) has also been reported as an important risk factor for both IPD and CAP [8,9].

Nowadays, COPD is a leading cause of morbidity and mortality worldwide. The prevalence of COPD increases with increasing age (approximately 1-3% in middle aged adults vs 6-10% in elderly people) and it is approximately three-fold higher in men than in women [10]. Likely, the prevalence of COPD is underestimated given the absence of systematic investigations in clinical practice for those patients with apparently non-severe or trivial symptoms. It has been estimated that approximately 15-25% people over 45 years-old have a moderate obstructive ventilatory disorder [11]. If we consider mortality, according to World Health Organization estimates, COPD is the fourth leading cause of death worldwide, with more than 2.7 million deaths in 2000 [12].

Incidence data of pneumococcal infections focused on COPD patients is scarce but, given these persons are considered to be at risk of pneumococcal infections, incidence is believed to be very large. Among patients with pneumonia, COPD is the most commonly reported comorbidity. Among COPD patients with pneumonia, hospital admission increases with the intensity of airflow obstruction [9,13-16].

Numerous studies have reported that COPD patients are at increased risk of pneumococcal disease (including CAP and IPD) compared with those without COPD.[13,17-19] In this way, Odds Ratios (**ORs**) ranging from 1.3-13.5 for CAP and 1.3-16.8 for IPD have been reported in COPD patients as compared with persons without COPD [9,14,15,17].

The incidence of all-cause pneumonia among people with COPD is around 40-50 cases per 1000 patients-year (approximately 3-4 fold greater than in the general population). In the United States, the reported annual incidence of hospitalization for CAP was 11 cases per 1000 among the general population over 65 years-old and 41 cases per 1000 among those patients with chronic lung diseases [20]. In Europe, incidences of 14 and 46 episodes per 1000 person-year have been reported among the general population and COPD patients, respectively [21,22]. Pneumococcus remains the most common microorganism identified among patients with chronic respiratory diseases with CAP [23,24] although Gram-negative bacilli are increasing in patients with severe obstruction [25,26]. Incidences of laboratory-confirmed pneumococcal CAP ranged from 0.5 to 2.1 per 1000 in the general population and 0.7 to 5.9 per 1000 among patients with chronic pulmonary disease [20-22,27] of which approximately 25% were bacteremic and 75% non-bacteremic cases. These figures are likely to be an underestimation of the true incidence of pneumococcal bacteremia because they do not take into account persons from whom blood cultures were never obtained or those where the culture was performed after the start of antibiotic therapy. In addition, those patients with COPD who develop pneumonia have more severe pneumonia and therefore are admitted to the intensive care unit more frequently and have significantly higher 30-day mortality than non-COPD patients [25,28].

Acute exacerbations (although they represent a less serious illness than CAP) are also an important cause of morbidity and mortality in COPD patients [11,29,30]. Approximately 50% of acute exacerbations in chronic bronchitis are triggered by bacterial infection [31] being pneumococcus responsible for almost a third of bacterial acute exacerbations [32]. There is an increased risk of exacerbations in COPD patients with persisting bacterial colonization in the respiratory tract, especially in COPD patients with pneumococcal colonization. It has been reported that pneumococcus was recovered from sputum in 33% of patients with COPD exacerbation [33].

Immunizations with influenza and pneumococcal vaccines (together with smoking cessation, inhaled long-acting bronchodilators or inhaled corticosteroids) are a variety of strategies that may be effective in order to reduce incidence of pneumonia and acute exacerbations in COPD patients [34-37].

The major aim of this article is to provide an overview of the different antipneumococcal vaccines, with reference to advantages and possible benefit for COPD patients.

TYPES OF ANTIPNEUMOCOCCAL VACCINES

The pneumococcus is surrounded by a polysaccharide capsule, and differences in this capsule permit serological differentiation into distinct serotypes [38]. However, the existence of more than 90 distinct serotypes (differing in their chemical composition, potential immunogenicity and epidemiological impact on different population groups) has greatly complicated the development and evaluation of anti-pneumococcal vaccines.

At the moment, there are 3 established approaches to anti-pneumococcal vaccination: capsular polysaccharide Pneumococcal Vaccines (**PPV**), Protein-Polysaccharide Conjugate Pneumococcal Vaccines (**PCV**) and Protein-Based Pneumococcal Vaccines (**PBPV**). At present, only the “old” 23-valent PPV and the “new” 13-valent PCV are available in clinical practice for use in adults. New PCVs including more serotypes (pre-licensed PCV15) will be available in few years.

Pneumococcal Polysaccharide Vaccine (PPV)

The classical 23-valent polysaccharide pneumococcal vaccine (PPV23) was licensed in 1983 and is usually recommended for all elderly people and some at-risk groups including those with chronic respiratory diseases. The vaccine contains capsular polysaccharide antigens from the 23 most dominant serotypes among clinical isolates of *S. pneumoniae*, accounting for approximately 80-90% of overall invasive infections in the adult population when the vaccine was licensed. These antigens induce type-specific antibodies (by a T cell-independent mechanism) that enhance opsonization, phagocytosis and killing of pneumococci by phagocytic cells [39].

Antibody response is generally satisfactory after PPV23, but children aged <2 years and immunodeficient persons do not consistently develop immunity, and certain high-risk individuals (including some people with medical co-morbidities and elderly individuals) may respond poorly [37,39,40].

Following vaccination there is a slow but steady decline in serotype-specific antibody titres, and pre-vaccination levels are generally reached within 5-10 years [41,42]. An anamnestic response does not occur at revaccination, although there is a significant increase in antibody levels (sometimes slightly lower than after the primary dose) [40,43]. Revaccination is only recommended for those persons who received PPV23 before 65 years of age, but its clinical effectiveness has not been clearly proved [43].

Despite many studies of PPV23 efficacy in different populations, few Randomized-Controlled Trials (**RCTs**) have focused specifically on COPD patients, [27,44-49] and they have reported inconclusive results. Outcome measures in the different trials were very heterogeneous and included pneumonia, acute exacerbations, change in lung function, hospital admissions or visits to the emergency department and mortality (includes mortality from respiratory disease, causes

other than respiratory disease and all-cause mortality). The heterogeneity of outcomes reported in the distinct trials, together with the low accuracy of the criteria diagnosis for COPD (not verified by spirometric data in some trials), largely limits the comparison of the different results and their interpretation.

In the largest RCT on PPV efficacy in COPD patients published to date, Alfageme et al [27] analyzed the efficacy of PPV in a RCT including 596 Spanish patients with spirometric diagnosis of COPD (298 receiving PPV23 and 298 receiving placebo), concluding that the efficacy of vaccination depends on the age and the severity of airflow obstruction. Considering overall study population, in Alfageme's trial, no differences in the risk of all-cause pneumonia was observed in vaccinated as compared with control subjects (OR: 1.03; 95% CI: 0.64-1.67). In subgroup analyses including only cases due to pneumococcus (5 cases) or unknown etiology (53 cases) pneumococcal vaccination appeared effective among subjects under 65 years (OR:0.24; 95% CI: 0.07-0.80), but it did not appear efficacious among COPD patients 65 years or older (OR: 1.14; 95% CI: 0.62-2.07). Among those patients with severe functional obstruction (forced expiratory volume in 1 second <40%) vaccination appeared to be more efficacious (OR: 0.52; 95% CI: 0.20-1.07), with greatest efficacy in younger patients with severe airflow obstruction (OR: 0.09; 95% CI: 0.01-0.65) [27].

In 2006, Granger et al [50] published the first Cochrane systematic review on PPV23 efficacy focused on COPD patients, concluding that PPV was not effective in this population to reduce all-cause pneumonia (OR: 0.89; 95% CI: 0.58-1.37) or all-cause mortality (OR: 0.94; 95% CI: 0.67-1.33).

In 2010, Walters et al [51] updated the Cochrane review including a total of 7 RCTs in their meta-analysis specifically focused on COPD patients. According this meta-analysis, in six studies involving 1372 people, the reduction in the risk of developing pneumonia among vaccinated compared to control did not achieve statistical significance (OR: 0.72; 95% CI: 0.51-1.01). The reduction in likelihood of acute exacerbations of COPD from two studies involving 216 people neither reached statistical significance (OR: 0.58; 95% CI: 0.30-1.13). Of the secondary outcomes for which data were available there was no statistically significant effect for reduction in hospital admissions (two studies) or emergency department visits (one study). Considering mortality, according to three studies involving 888 people followed during periods up to 48 months post-vaccination, there was no significant reductions in the risk of all-cause death (OR: 0.94; 95% CI: 0.67-1.33), or death from cardio respiratory causes (OR: 1.07; 95% CI: 0.69-1.66). The authors concluded that, while it is possible that PPV may provide some protection against morbidity in persons with COPD, no significant effect on any of the outcomes was shown in the meta-analysis, recommending that further large RCTs in this population would be needed to confirm the effectiveness of the vaccine suggested by results from some individual studies.

Although nonRCTs have inherent limitations (especially the possibility of selection bias), they can provide interesting data on the effectiveness and impact of the vaccination. In this way,

several observational studies have reported benefits using the PPV23 in patients with chronic respiratory diseases [22,52-54].

On other hand, considering the limited data about efficacy/effectiveness of the PPV23 in COPD patients, data on PPV23 efficacy in the general population have also been used to establish vaccine recommendations for these patients [55-64]. The Cochrane review on PPV efficacy/effectiveness among the general population recommends the use of PPV to prevent IPD in adults (particularly otherwise healthy adults), but it also concluded that the meta-analysis did not provide compelling evidence to support the routine use of PPV to prevent pneumonia or death [62,64]. This meta-analysis demonstrates strong evidence of protection against IPD, with an efficacy of 74% (95% CI 56% to 85%) in RCTs and an effectiveness of 52% (95% CI 37% to 61%) in observational studies (case-controlled and cohort studies). Vaccine efficacy appears poor amongst the subgroup of adults with chronic diseases, where vaccination efficacy did not reach statistical significance. In relation to all-cause pneumonia (the most reported outcome in the Cochrane review, the meta-analysis showed that the PPV provides an apparent protective efficacy of 29%, although substantial statistical heterogeneity was observed (OR: 0.71; 95% CI: 0.52-0.97) [62,64].

Several studies have shown that the PPV23 is cost-effective for preventing IPD among the general population over 65 years in developed countries, [65,66] but there is no data about cost-effectiveness of vaccination among COPD patients given the lack of efficacy data in these persons.

In general, because the risks of immunization are believed to be very small, public policy at this time continues to support antipneumococcal vaccination with PPV23 for all patients with chronic lung diseases regardless of age [67].

Current CDC's recommendations for using PPV-23, besides COPD, include smoking and asthma. Revaccination (5-10 years after prime dose) is recommended for those persons who received PPV-23 before 65 years of age [67]. It must not be forgotten, however, that the PPV-23 provides incomplete protection, it does not elicit long-lasting immunity, and no anamnestic effect occurs at revaccination. So, more effective vaccination strategies would be needed.

Pneumococcal Conjugate Vaccine (PCV)

Given the poor immunogenicity of PPV23 in children, extensive efforts were made at the end of the past century to develop a new generation of pneumococcal vaccines with good immunogenicity in infants. The result was a protein-polysaccharide combination, known as Pneumococcal Conjugate Vaccine (**PCV**), which included some selected polysaccharides bound to a protein carrier. This renders the vaccine T-cell-dependent, and thus capable of stimulating antibody responses and priming for a memory response on rechallenge. The first available PCV contained specific antigen for the 7 most common pneumococcal serotypes in USA children, and was licensed for paediatric use in 2000 [68].

In contrast to the polysaccharide vaccine, which only had shown a limited impact on the overall disease burden, the introduction of the PCV-7 as routine vaccination for infants provided initially very encouraging results, with sustained reduction on the incidence of IPD among children (direct effect) but also in adults (indirect effect by herd immunity reducing the transmission of PCV-7 strains in the population) [60-70,71,72].

Later, several years after PCV7 introduction, a serotype replacement phenomenon was observed, with increasing rates of nonPCV7 serotypes [73,74] and then, two new PCVs (including progressively more serotypes) were licensed in 2009 (PCV10) and 2010 (PCV13) to replace the “earlier” PCV7 among children.

PCV13 was licensed by the Food and Drug Administration (**FDA**) for prevention of IPD and otitis media in infants and young children in February 2010 [75]. Considering the good immune response and efficacy shown in children, it was proposed that the use of the conjugate vaccine could improve antibody responses and clinical efficacy in high-risk adults with poor response to PPV23. In 2011, FDA and EMA (European Medicines Agency) licensed PCV13 for prevention of pneumonia and IPD in adults aged ≥ 50 years [76,77]. The license for adult use was granted under FDA’s accelerated approval pathway. Thus, despite there was not data on clinical efficacy/effectiveness in adults, approval of PCV13 for adults was based on immunogenicity studies that demonstrated better or non-inferior antibody responses to PCV13 as compared with PPV23 among adults (which reasonably predicted clinical benefit).

An important immunological consequence of conjugation of polysaccharide antigen with a carrier protein is that the CD4+ helper T-cell fraction contributes to the immunological response. Thus a T-cell-dependent response is generated, with predominant IgG1 and IgG3 antibodies, instead of the T cell-independent antibody response that occurs with simple polysaccharide antigens [78]. This is an important theoretical advantage for the conjugated vaccine, given that the response to polysaccharide antigens is much more varying and age-dependent, and antibody levels therefore more uncertain than with conjugated antigens. Thus, as in young children, it could be expected that some high-risk adults (especially immunocompromised persons) obtain a benefit from using the conjugate vaccine.

Based on immunogenicity data, [79,80] together with an anticipated clinical efficacy, on June 2012, the Advisory Committee on Immunization Practices (**ACIP**) recommended PCV13 (plus PPV23) for adults with high-risk conditions such as cochlear implants, CSF leaks, functional or anatomic asplenia and/or immunocompromising conditions [81]. Later, on September 2014, ACIP added a recommendation for dual vaccination with PPV23+PCV13 for all persons aged 65 years or more [82].

Nevertheless, we note again that when PCV13 was licensed for using in adults, clinical trial data (efficacy/effectiveness) was not yet available for PCV13 among adult populations.

The ACIP's recommendations were made on the basis of clinical benefit anticipated by the CAPITA trial. This RCT, which final results were not published until March 2015, [83] reported an efficacy of 75% against IPD and 46% against nonbacteremic pneumococcal pneumonia due to vaccine serotypes. Concretely, the CAPITA trial (a RCT evaluating PCV13 vs placebo among 85,000 individuals 65 years or older with a mean follow-up of 3,97 years in the Netherlands) has reported that vaccine-type community-acquired pneumonia occurred in 49 persons in the PCV13 group and 90 persons in the placebo group (vaccine efficacy, 45.6%; 95.2% confidence interval [CI], 21.8 to 62.5), nonbacteremic and noninvasive community-acquired pneumonia occurred in 33 persons in the PCV13 group and 60 persons in the placebo group (vaccine efficacy, 45.0%; 95.2% CI, 14.2 to 65.3), and invasive pneumococcal disease occurred in 7 persons in the PCV13 group and 28 persons in the placebo group (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8). All-cause community-acquired pneumonia occurred in 747 persons in the PCV13 group and 787 persons in placebo group (vaccine efficacy, 5.1%; 95% CI, -5.1 to 14.2) [83]. Interestingly, efficacy data reported for the PCV13 in the CAPITA trial are essentially similar to efficacy data estimated for the PPV23 in the last Cochrane meta-analysis) [64]. If we consider specifically the subgroup of COPD patients, the CAPITA trial has not reported disaggregate results according to patients with respiratory or pulmonary diseases; so, PCV13 effectiveness in COPD patients remains unknown.

Of note, we highlight that the CAPITA trial has not proved significant effectiveness of vaccination in the subgroup of immunocompromised patients (persons where PCV13 is especially recommended). On other hand, we also note that in the CAPITA trial the total number of prevented cases was relatively low (concretely, 21 IPD cases and 27 nonbacteremic pneumococcal pneumonia cases considering a total study population of more than 300,000 person-year at observation). Consequently, despite some studies have concluded in favour of PCV13 cost-effectiveness among adults, [84] the above mentioned CAPITA's data does not suggest a good level of cost-effectiveness of PCV13 vaccination in adults [85-87].

To date, ACIP recommends dual antipneumococcal vaccination (using PCV13 plus PPV23) for persons aged 65 years or older (with or without underlying conditions) and persons 19-64 years with certain high-risk conditions (basically anatomyc or functional asplenia and/or immunocompromising conditions) [81,82]. At present, ACIP recommends antipneumococcal vaccination using exclusively PPV23 for persons 19-64 years with certain co morbidities or risk conditions (including COPD, asthma, chronic heart disease, diabetes mellitus, alcoholism and smoking) [67].

In relation with possible interactions with other vaccines, it has been shown that the concomitant administration of PCV13 and trivalent inactivated influenza vaccine might diminish the antibody response to PCV13 [88]. Therefore, it would be recommended to administer these vaccines in different visits.

Experimental Protein-based Pneumococcal Vaccines (PbPV)

Considering that both PPV and PCV only elicit protective antibodies against the infection of serotypes that are included in the vaccines, efforts are currently being made to design and develop a new generation of anti-pneumococcal vaccines with theoretical full protection against all pneumococcal serotypes. These new generation vaccines, known as protein-based pneumococcal vaccines (PbPV), would be composed by distinct capsular pneumococcal proteins or virulence factors [89,90].

Numerous PbPV candidates are being investigated by several groups with promising results against invasive infections and nasopharyngeal carriage in animal models. Main investigated proteins include Pneumococcal surface protein A (**PspA**), Pneumococcal surface adhesion A (**PsaA**), Pneumococcal histidine triad protein (**Pht**) and pneumolysin [90]. It has been reported that the combination of distinct proteins with different protective functions could increase the vaccine protection [90]. Genome sequencing of bacteria may also represent a powerful way to develop novel potential recombinant vaccines [91].

Besides the possibility of full protection against all pneumococcal serotypes, major potential advantages for a future PbPV include the possibility of oral or intranasal administration, and probably a less complex production process and lower cost than for conjugate vaccines. If it is found that these proteins cannot provide sufficient protection as a sole component of the vaccine, it is possible that they could be used either as a carrier protein for a conjugate vaccine or as a supplement component of current polysaccharide vaccine to provide additional protection [90,91]. A common protein vaccine with broad protection against pneumococcus could be available in the next 5-10 years [92].

CURRENT ANTIPNEUMOCOCCAL VACCINATION RECOMMENDATIONS

At present, considering current scientific evidence, antipneumococcal vaccination is a reasonable option to prevent pneumococcal infections among immune competent adults, although the evidence is lower for those patients with certain degree of immune compromise and/or co morbidities [55-64].

Considering specifically COPD patients, despite patients with chronic respiratory diseases are commonly described as an at-risk population for pneumococcal infections, controlled studies on pneumococcal vaccination efficacy in such patients are very limited and largely underpowered to obtain clear evidence about vaccination benefits [50,51].

Most meta-analyses have concluded that the PPV23 is effective against IPD among immune competent persons; recommendations for vaccinating COPD patients with PPV23 are based on this data, although the evidence for vaccine efficacy is less clear among persons with co morbidities [55-64]. If we consider PCV13, recommendations for its use in COPD patients are based on

efficacy data observed in the general elderly people (since there is not efficacy/effectiveness data specifically evaluated in COPD patients to date) [83].

A dose of the classical PPV23 is generally recommended for older adults and high-risk individuals, including patients with COPD and asthma [67,93]. A second dose of PPV23 is also recommended for patients under 65 years-old [67]. The “new” PCV13 is recommended (together with the PPV23) for those patients who have some immunocompromising conditions [67,93]. Some experts recommend PCV13 for all COPD patients (not only immunocompromised), but there is not consensus about this recommendation. When dual vaccination with PPV23 and PCV13 is needed, PCV13 followed by PPV23 eight weeks later is preferable. Alternatively, PPV23 followed by PCV13 at least one year later may also be prescribed [81,82].

If we consider current recommendations of the Advisory Committee on Immunization Practices of the Centers for Diseases Control and Prevention, a sequential dual antipneumococcal vaccination (PPV23+PCV13) is recommended for persons aged 65 years or older (with or without underlying conditions) and persons 19-64 years with CSF leaks, cochlear implants, functional or anatomic asplenia, sickle cell disease or other hemaglobinopathy, congenital or acquired asplenia, immunocompromised persons (congenital or acquired immunodeficiency [includes B-humoral] or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)], human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immune suppression [treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy], solid organ transplant and multiple myeloma) [81]. At present, ACIP recommends antipneumococcal vaccination using exclusively PPV23 for immune competent persons 19-64 years with certain co morbidities or risk conditions (including COPD, asthma, chronic heart disease, diabetes mellitus, alcoholism and smoking) [67].

CONCLUSION

Pneumococcal infections remain a major cause of morbidity and mortality worldwide. Patients with chronic obstructive pulmonary disease are at increased risk of both non-invasive and invasive pneumococcal diseases and community-acquired pneumonia. Thus, antipneumococcal vaccination could prevent pneumococcal infections and reduce the risk of mortality in both immune competent and immunocompromised COPD patients.

To date, there are two available preventive options against pneumococcal infections for using in adults, the “classical” 23-valent pneumococcal polysaccharide vaccine and the “new” 13-valent pneumococcal conjugate vaccine, but neither is optimal. Key advantages and shortcomings for both vaccines are summarized in Table 1.

Table 1: Advantages and Limitations for Using PPV23 Or PCV13 in COPD Patients.

Vaccine	Advantages	Limitations
PPV23	<ul style="list-style-type: none"> · Long experience (licensed in 1983). · Few expensive. · Considerable vaccine-serotype coverage to prevent IPD in adults at present (approximately 50-70%). · Efficacy demonstrated against vaccine-type IPD (approximately 65-75%) in immunocompetent adults. · Efficacy proven against pneumonia in a RCT focused specifically on COPD patients. · Cost-effective for the general older adult's population even if it only prevents IPD. 	<ul style="list-style-type: none"> · Immune response after PPV23 can be weak in some individuals (especially among immunocompromised people or those with major comorbidities) · It does not elicit long-lasting immunity and no anamnestic effect occurs at revaccination (T cell-independent immune response) · Controversial protective effect against nonbacteremic pneumonia. · Uncertain cost-effectiveness focused specifically on COPD patients. · No effect on nasopharyngeal carriage. · Little or no impact in reducing overall pneumococcal disease burden.
PCV13	<ul style="list-style-type: none"> · T-cell-dependent immune response (larger duration and boosting effect at revaccination) · Efficacy against vaccine type IPD (75%) and nonbacteremic pneumococcal pneumonia (approximately 45%) demonstrated in a RCT focused on elderly persons. · Potential protective effect in reducing nasopharyngeal carriage. · Protective indirect effect (by herd immunity) among nonvaccinated persons. 	<ul style="list-style-type: none"> · Short experience (approved in 2010 for children and 2012 for adults). · Expensive. · No available efficacy data in COPD patients at present. · No available consistent cost-effectiveness data for COPD patients at present. · Relatively small serotype-coverage for IPD cases among adults (approximately 30-50%). · Possibility of serotype replacement phenomenon in next years. · Future reduction of vaccination impact in adults (including COPD patients) because of probable indirect effects from PCV13 pediatric routine use.

The main advantage for the PCV13 is the fact that it has better immunogenicity than PPV23, but a major shortcoming is the fact that it is directed against strains that are likely to be greatly reduced in the population since its introduction in childhood immunization. The main shortcoming for the PPV23 is its poor immunogenicity than PCV13 but, as major advantage, it may provide protection against ten additional serotypes.

In contrast with the polysaccharide vaccine (T-cell-independent immune response), protein-polysaccharide conjugate vaccines promise to enhance the immune response due to their T cell-dependent mode of action, but there is no data on PCV13 efficacy/effectiveness among COPD patients yet.

Apart from its possible better immunogenicity/efficacy than PPV23, the relatively low serotype coverage of the PCV13 is an important shortcoming for routine use of PCV13 alone in adult populations. A sequential strategy using both PCV13 and PPV23 vaccines could be a way to achieve greater effectiveness among high-risk people, but its possible cost-effectiveness is uncertain.

We note that, despite patients with chronic respiratory diseases have been commonly described as an at-risk population for pneumococcal infections, and pneumococcal vaccination has been recommended by the major COPD guidelines, studies on pneumococcal vaccination efficacy in such patients are very limited and vaccine efficacy and cost-effectiveness remains controversial.

At present, the following recommendations can be made for COPD patients: a) those COPD patients with immunocompromising conditions (i.e., steroids or immune modulating therapy, current sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, human immunodeficiency virus infection/acquired immunodeficiency syndrome, nephrotic syndrome, and hematologic or solid malignancies) should receive dual vaccination with PCV13 and PPV23 (preferably PCV13 followed by PPV23 eight weeks later or, alternatively, PPV23 followed by PCV13 at least one year later); b) for those COPD patients without the above mentioned conditions, according to the Advisory Committee on Immunization Practices (**ACIP**), dual vaccination is unnecessary and they should receive only a dose of PPV23 (with a second dose for revaccination at 5-10 years after receipt prime PPV23 in those COPD patients aged less than 65 years).

COPD patients aged 18-64 years without immunocompromising conditions, where PCV13 is currently not recommended, could obtain an individual benefit from dual vaccination with PPV23+PCV13, but the cost effectiveness of this strategy seems low.

Serotype replacement phenomenon will probably occur using PCV13 and, likely, new PCVs with broader serotype coverage will be needed at medium-term. In this way, a PCV15 is been evaluated in prelicensure studies in children and adults [94,95]. Nevertheless, the serotype replacement phenomenon cannot be fully overcome by increasing the number of serotypes in the vaccine, therefore new technologies, such as protein-based vaccines, are greatly needed. Protein-based vaccine offers the potential advantage of a serotype-independent protection and several are in various stages of investigation. A common protein vaccine with broad protection against pneumococcus could be available in the next 5-10 years.

Meanwhile, immune competent COPD patients should receive PPV23 (with revaccination at 5-10 years) and immunocompromised COPD patients should receive dual vaccination with PCV13 and PPV23.

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