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Antipneumococcal Vaccination in COPD Patients

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1. 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 heart or pulmonary disease (Kyaw 2005).

The main reservoir of pneumococci is the nasopharynx, and the possible outcomes after colonisation 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 (Feikin 2000, Baddour 2004). Figure 1 illustrates the overlap between overall community-acquired pneumonia, pneumococcal pneumonia 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-year in a multicentre study carried out in five countries (Kalin 2000). 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 (Orqvist 2005).

Chronic obstructive pulmonary disease (COPD) is a major risk factor for community-acquired pneumonia, and smoking (the most common cause of COPD) has been reported as an important risk factor for IPD (Torres 1996, Nuorti 2000).

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 (Murtagh 2005). Likely, the prevalence of COPD is underestimated given the absence of systematic
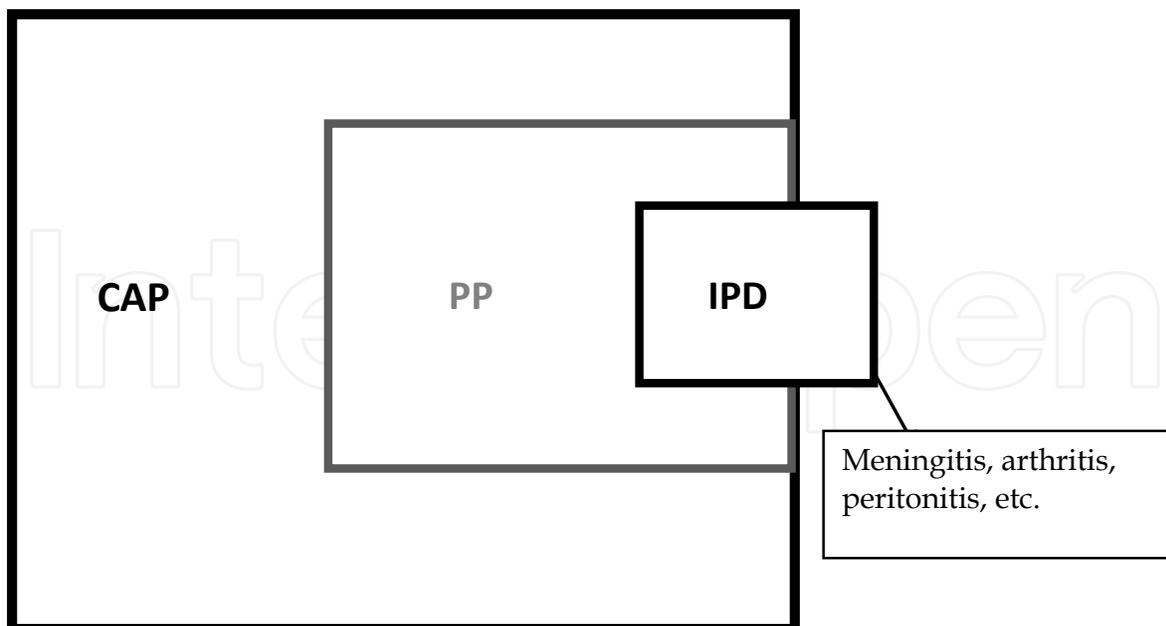
Fig. 1. Overlap between overall community-acquired pneumonia (CAP), pneumococcal pneumonia (PP) and Invasive Pneumococcal Disease (IPD).

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 (GOLD 2008). If we consider mortality, a according to World Health Organization estimates, COPD is the fourth leading cause of death worldwide, with more than 2.7 million deaths in 2000 (NHLBI 2001).

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. 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 hospitalisation 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 (Jackson 2003). In Europe, incidences of 14 and 46 episodes per 1000 person-year have been reported among the general population and COPD patients, respectively (Vila-Corcoles 2006, Ochoa-Gondar 2008). Pneumococcus remains the most common microorganism identified among patients with chronic respiratory diseases with CAP (Liebermen 2002, Mandell 2007) although Gram-negative bacilli are increasing in patients with severe obstruction (Restrepo 2008, Ko 2008). 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 (Jackson 2003, Vila-Corcoles 2006, Alfegeme 2006, Ochoa-Gondar 2008) 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 (Restrepo 2008, Molinos 2009).

Acute exacerbations (although they represent a less serious illness than CAP) are also an important cause of morbidity and mortality in COPD patients (NICE 2004, Papi 2006, GOLD 2008). Approximately 50% of acute exacerbations in chronic bronchitis are triggered by bacterial infection (Sethi 2000) being pneumococcus responsible for almost a third of bacterial acute exacerbations (Saint 2001). There is an increased risk of exacerbations in COPD patients with persisting bacterial colonisation in the respiratory tract, especially in COPD patients with pneumococcal colonisation. It has been reported that pneumococcus was recovered from sputum in 33% of patients with COPD exacerbation (Bogaert 2004).

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 (CDC 1997, Black 2004, Poole 2009, Varkey 2009).

2. Types of antipneumococal vaccines

The pneumococcus is surrounded by a polysaccharide capsule, and differences in this capsule permit serological differentiation into distinct serotypes (Hausdorff 2005). 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) (Fedson 2003, Abraham Van-Parijs 2004, Tai 2006). At present, only the "old" PPV-23 for use in adults and two "new" PCVs (PCV-10 and PCV-13), both licensed in 2010 for use in children, are available in clinical practice.

2.1 Pneumococcal polysaccharide vaccine

The currently available PPV-23 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. These antigens induce type-specific antibodies (by a T cell-independent mechanism) that enhance opsonization, phagocytosis and killing of pneumococci by phagocytic cells (Fedson 2003).

Antibody response is generally satisfactory after vaccination, 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 (Sankilampi 1996, CDC 1997, Fedson 2003). 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. 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) (Sankilampi 1996, Artz 2003). Revaccination is only recommended for those persons who received PPV-23 before 65 years of age (CDC 1997) but its clinical effectiveness has not been clearly proved (Artz 2003).

Despite many studies of PPV efficacy in different populations, few randomized-controlled trials (RCTs) to date were focused on COPD patient (Leech 1987, Davis 1987, Alfageme 2006, Steentoft 2006, Ya Tseimakh 2006, Teramoto 2007, Furumoto 2008) and they have reported unconclusive 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 heterogenity 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 two earlier RCTs published in 1987 evaluating a 14-valent PPV, Davis et al and Leech et al did not observe any efficacy of pneumococcal vaccination, but these negative results were attributed to the small number of patients included in the series and the low rate of pneumococcal bacteremia. Importantly, before vaccination, antibody titers were higher among the COPD patients than among the healthy control subjects in both trial, which suggests previous pneumococcus exposure and largely limits possible conclusions on vaccine efficacy in this population (Leech 1987, Davis 1987).

In the largest RCT on PPV efficacy in COPD patients published to date, Alfageme et al analysed the efficacy of PPV in a RCT including 596 Spanish patients with spirometric diagnosis of COPD (298 receiving PPV-23 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) (Alfageme 2006).

In a short trial including 49 COPD patients, Steentoft et al observed that a rise in antibody levels after PPV-23 occurred among patients with COPD despite the use of systemic steroid treatment, but a statistically significant clinical effect of vaccination was not demonstrated. In fact, no differences between vaccinated and control subjects were observed for the risk of pneumonia (OR: 0.59; 95% CI: 0.15-2.32), acute exacerbations (OR: 1.44; 95% CI: 0.29-7.14) or hospital admission (OR: 0.95; 95% CI: 0.26-3.48) (Steentoft 2006).

In 2006, Granger et al published the first Cochrane systematic review and meta-analysis on PPV 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) (Granger 2006).

In 2010, Walters et al uptated 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 cardiorespiratory causes (OR: 1.07; 95% CI: 0.69-1.66). The authors concluded that, while it is posible 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, recomending that further large RCTs in this population would be needed to confirm the effectiveness of the vaccine suggested by results from some individual studies (Walters 2010).

In the present authors opinion, all RCTs on PPV efficacy focused in COPD patients has been largely underpowered considering that the most large RCT (Alfageme 2006) included less than six hundred patients (with only five definitive pneumococcal pneumonias observed during 3-year follow-up). Furthermore, given the effectiveness of the vaccine in protecting individuals against IPD, commencing new RCTs in populations at risk where vaccine effectiveness and disease burden is known would create ethical difficulties. Thus, 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 PPV-23 in patients with chronic respiratory diseases (Nichol 1999, Ochoa-Gondar 2008, Watanuki 2008, Sumitani 2008).

On other hand, given COPD is not a cause of immunodepression (apart from the impairment of local defences) and the reported antibody response is compatible with a vaccine efficacy despite its relatively rapid decline, data on efficacy in the general population can also be used to establish vaccine recommendations for these persons. Figure 2 shows point estimates of PPV efficacy against IPD, pneumonia and death according to the two last published meta-analyses (Moberley 2008, Huss 2009).

The last 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. 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) (Moberley 2008).

We note the limited amount of data regarding persons with chronic pulmonary diseases. Considering RCT's data, vaccination of younger patients with COPD appears best supported, while the evidence of a benefit to older patients is weaker. However, given
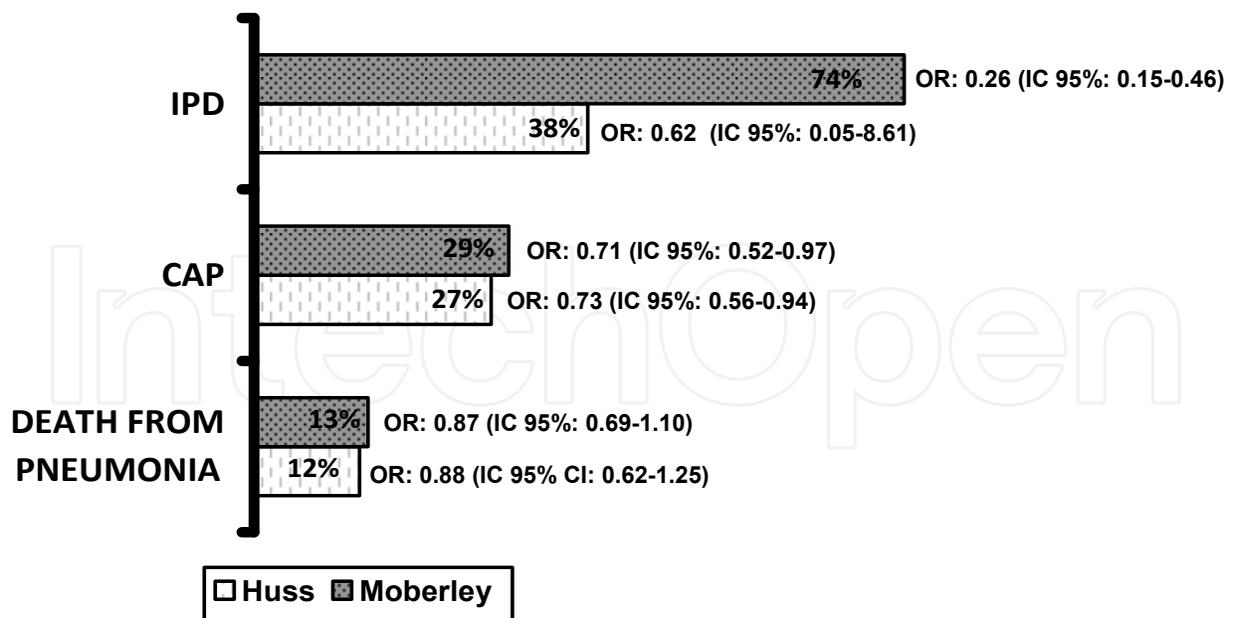
Fig. 2. Estimation of PPV efficacy against IPD, pneumonia and death according to the two last published meta-analyses (Moberley 2008, Huss 2009).

observational studies, PPV also appears effective in older patients with COPD. Because the risks of immunization are believed to be very small, public policy at this time continues to support immunization of all patients with chronic lung diseases regardless of age (CDC 1997, CDC 2010). New CDC's recommendations for using the PPV in adults have been publihsed in 2010. The CDC's new recommendations include some changes from 1997 recommendations.the indications for which PPV-23 vaccination is recommended now include smoking and asthma(CDC 2010).

2.2 Pneumococcal conjugate vaccines

Given the poor immunogenicity of PPV in children, extensive efforts have been made 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 contains 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 firstly available PCV contained specific antigen for the 7 most common pneumococcal serotypes in children, and was licensed for paediatric use in 2000 (Black 2000).

In contrast to the PPV-23, which only had a limited impact on the overall disease burden, the introduction of the PCV-7 as routine vaccination for infants has provided very encouraging results, even reducing incidences of pneumococcal disease in unvaccinated people (by herd immunity reducing the transmission of PCV-7 strains in the population) (Whitney 2003, Hicks 2007). In addition, an important reduction in drug-resistant Streptococcus pneumoniae isolates has been observed in all-age groups after the introduction of PCV-7 for children (Kyaw 2005).

Among people over 50 years in the United States, IPD declined by 28% (from 40.8 to 29.4 per 100,000 person-year between 1998-2003) (CDC 2005) with further reductions in recent years

(Pilishvili 2010). Nevertheless, it must be noted that for some groups of older adults the reduction was somewhat lower. There was only a very modest reduction in the number of cases in subjects with comorbid conditions, such as chronic renal disease, heart disease and chronic pulmonary disease (Lexau 2005, Lockhart 2006).

Considering the good immune response and efficacy shown in children, it has been proposed that the use of the conjugate vaccine could improve antibody responses and clinical efficacy in high-risk adults with poor response to PPV (Fry 2002, Lockhart 2006, Jackson 2008). 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 (Wuorimaa 2001). This is an important 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, adult population groups could obtain benefit from using a conjugate vaccine in the future.

Until now, the low serotype coverage has been a very important shortcoming for the "old" PCV-7, bbut he new PCVs including more serotypes (especially the PCV-13, which has broad serotype coverage for both children and adults) could be a good future alternative for all age groups (Scott 2008).

However, at the moment, there are important factors to consider before PCV could ever be used in adult populations. There are only limited immunogenicity data and no data on clinical efficacy in adults. Furthermore, it is not known how many doses of conjugate vaccine adults would require, what age groups should receive the vaccine, and what would be the optimal timing for pneumococcal conjugate vaccination (Abraham Van-Parijs).

2.3 Protein-based pneumococcal vaccines

Although the virulence of Streptococcus pneumoniae is largely dependent on its polysaccharide capsule, it has been demonstrated that numerous protein virulence factors are involved in the pathogenesis of pneumococcal disease (Orihuela 2004), and currently extensive efforts are being made to develop a new generation of pneumococcal vaccines. These vaccines, known as protein-based pneumococcal vaccines (PBPV), are composed of pneumococcal proteins or virulence factors, together with antibodies to them to neutralize their function and reduce the virulence of the infecting bacteria (Tai 2006).

Several formulations of experimental PBPV candidates containing different pneumococcal proteins (eg, PspA, PspC, Ply, or PsaA) have shown protective effects against invasive infections and nasopharyngeal carriage in animal models, and some studies assessing the development of natural antibodies after carriage and invasive disease in humans have reported development of an immune response against some of them (Tai 2006). It has been reported that the combination of various proteins with different protective functions may provide a broader protection (Ogunniyi 2007). Furthermore, other pneumococcal proteins identified very recently by exploiting molecular immunological techniques suggest interesting new vaccine directions (Giefing 2008).

Theoretical major advantages for a future PbPV could be the serotype-independent protection, the possibility of oral or intranasal administration, and probably a less complex production process and a lower cost than conjugate vaccines. However, at the moment, information on humans is scarce, and many studies and several years will be needed to elucidate the true potential of PbPV in human prevention. If finally these proteins can not provide sufficient protection as a sole component of the vaccine, it is posssible that they could be used either as a carrier protein for a conjugate vaccine or as a supplement component for the current vaccines to provide additional protection against pneumococcal infections (Wright 2008).

3. Conclusions

S. pneumoniae remains a major cause of morbidity and mortality worldwide. There are different preventive options but, at the moment, none is optimal. Among patients with chronic respiratory diseases, pending other more effective antipneumococcal vaccines, the PPV-23 (together with influenza vaccine) is currently the only preventive approach that has demonstrated an effect, even if it does not match up to expectations (Gaillat 2009).

COPD patients are commonly described as an at-risk population for pneumococcal infections, but RCTs on PPV efficacy in such patients are very limited and largely underpowered to obtain a reliable conclusion about the efficacy of the vaccine. Among the general population, most meta-analyses have concluded that the PPV is effective against IPD among immunocompetent persons. Recommendations for vaccinating COPD patients are based on this data, although the evidence for vaccine efficacy is less clear among persons with comorbidities.

Among COPD patients, the effectivenes of vaccination in preventing pneumonia and/or acute infective exacerbations is unclear. Two meta-analyses focused on COPD patients concluded that, although it is possible that PPV may provide some protection in persons with COPD, no significant protective effects were demonstrated in the meta-analysis. Considering nonRCTs, the clinical effectivenes of vaccination is also uncertain, but several studies have reported distinct benefits from pneumococcal vaccination in preventing distinct respiratory infections (using the PPV-23 alone and/or together with influenza vaccine).

Several studies have shown that the PPV-23 is cost-effective for preventing IPD among the general population over 65 years in developed counttries, but there is no data about cost-effectiveness of vaccination among COPD patients given the lack of efficacy data in these persons. 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. It must not be forgoten, 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 are needed.

In the next few years, the results of ongoing trials evaluating the efficacy of the PCVs in adults will be critical in determining the position of the conjugate vaccine in the prevention of pneumococcal diseases in patients with chronic respiratory diseases. In coming years, new PCVs including progressively more serotypes (most likely emerging types due to epidemiological changes) will probably be needed. However, the serotype replacement phenomenon can not be fully overcome by increasing the number of serotypes, so new

technologies, such as protein-based or genomic vaccines, will be greatly needed. Experimental protein-based pneumococcal vaccine candidates offer the potential advantage of serotype-independent protection and several are in various stages of development in animal models, but none can be expected to be available in clinical practice for several years at least.

Until better options are available, the PPV-23 should continue to be used in high-risk individuals, including younger and older adults with COPD. Although only moderately effective, the burden of pneumococcal disease is greatest in these persons and they can obtain benefit from vaccination.

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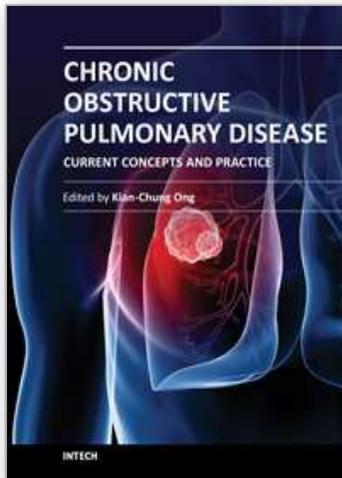
Chronic Obstructive Pulmonary Disease - Current Concepts and Practice

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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