Review

Prevention of Invasive Pneumococcal Disease (IPD)

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Key words:
- Invasive pneumococcal disease
- Pneumococcus
- Vaccination

Abbreviations:
IPD: Invasive pneumococcal disease
PPSV23: Pneumococcal polysaccharide vaccine
PCV13: Pneumococcal conjugate vaccine

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SUMMARY
***Streptococcus pneumoniae* consists of a major cause of community-acquired pneumonia in the elderly, resulting in considerable morbidity and mortality worldwide. Although pneumococcal community-acquired pneumonia presents usually as non-bacteremic disease, invasive pneumococcal disease (IPD) concerns infection of normally sterile sites, such as blood or cerebral fluid. The risk for Invasive Pneumococcal Disease increases in particular groups of patients, including hematologic malignancies, infection with human immunodeficiency virus (HIV), asplenia - functional or anatomic, chronic diseases and extreme ages (<4 and >65 years old). The prevention against IPD is achieved by vaccines against *Streptococcus pneumoniae.* Today, there are two available types of vaccines, the polysaccharide pneumonococcus vaccine (PPSV23 and the pneumonococcus conjugated vaccine (PCV13).**
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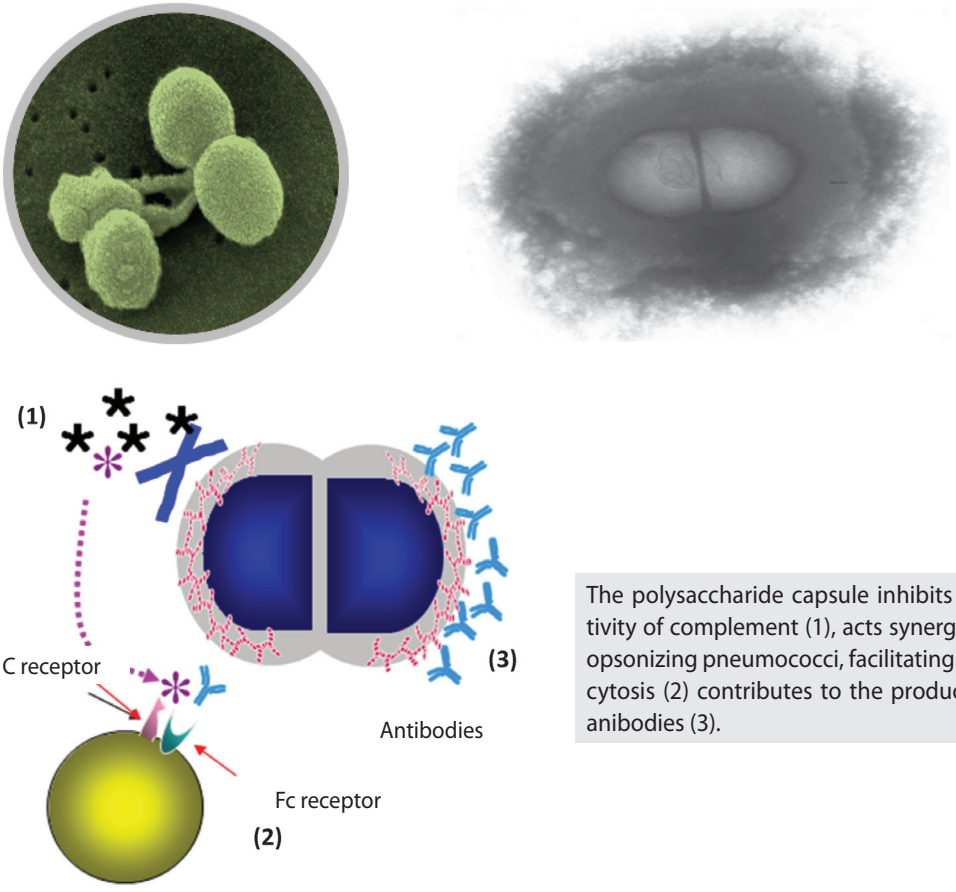
INTRODUCTION

Streptococcus pneumoniae consists of a major cause of community-acquired pneumonia in the elderly, resulting in considerable morbidity and mortality worldwide[1,4,5]. It is estimated that among all age groups, pneumococcal disease caused 1.6 million deaths annually[6]. While pneumococcal disease occurring in childhood is well understood, its burden among adults remains a clinical challenge impeding policy formulation for prevention and treatment[7].

Streptococcus pneumoniae is a lancet-shaped, gram-positive, facultative anaerobic organism. It was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. Typically, it is observed in pairs (diplococcus) but may also be found as singular or in short chains (Figure 1). Some pneumococci are encapsulated, with surfaces composed of polysaccharides. Encapsulated organisms are pathogenic for humans as capsular antigenic polysaccharides are the primary basis for the pathogenicity of the organism. The classification of pneumococci to serotypes is based on their capsular

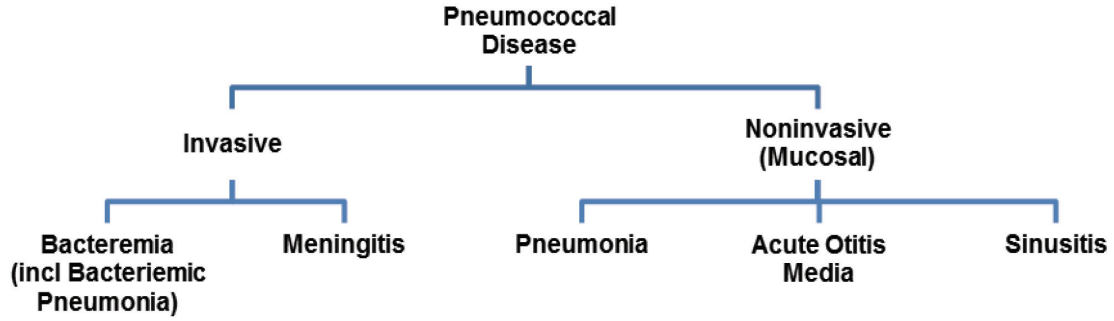


The polysaccharide capsule inhibits the activity of complement (1), acts synergically in opsonizing pneumococci, facilitating phagocytosis (2) contributes to the production of anibodies (3).

FIGURE 1. *Streptococcus pneumoniae* (diplococci)and the polysaccharide capsule.

polysaccharides. Pneumococci express over 90 capsular serotypes, which have different potential to cause disease[8-11]. Although pneumococcal community-acquired pneumonia occurs usually as non-bacteremic disease, invasive pneumococcal disease (IPD) concerns infection of normally sterile sites, such as blood or cerebral fluid, occurring in approximately 25% of cases[4,7] (Table 1). The majority of IPD cases (80%) present with bacteremic

TABLE 1. Classification of pneumococcal disease



[1]Instead of the term «non invasive» pneumonococcal disease, it is also used the term "mucosal"

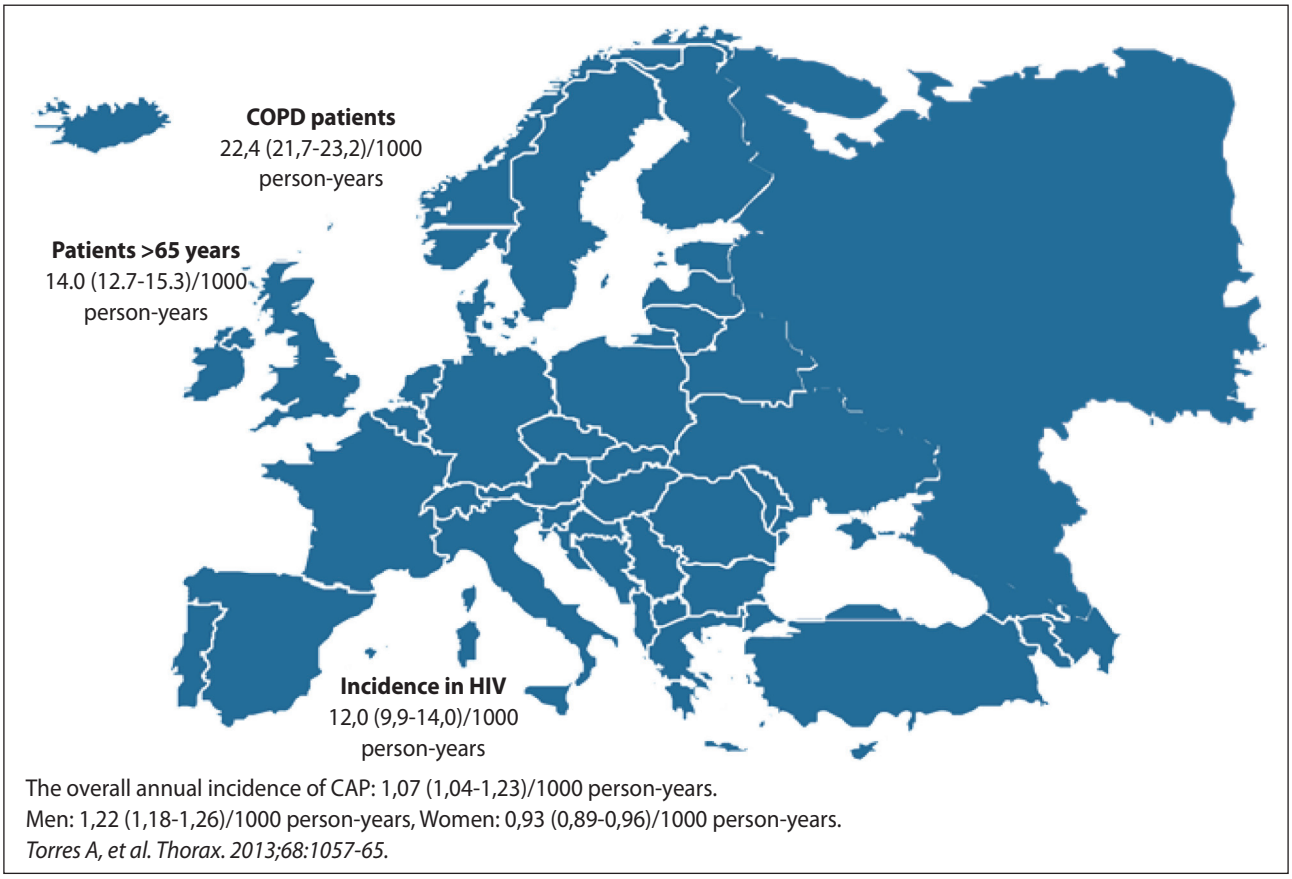
[2]Non invasive pneumococcal disease can be evolved to invasive disease, eg in some cases after pneumonia, bacteremia from *Str. pneumoniae* can be appeared.

pneumonia whilst 25-30% of patients with pneumococcal pneumonia experience pneumococcal bacteremia[2].

The aim of this article is to underline the importance of prevention of IPD through vaccination, as well as to elucidate the main differences of the two available vaccines regarding their efficacy and immunogenicity.

IPD: INCIDENCE AND RISK FACTORS

More than 12,000 cases of pneumococcal bacteremia without pneumonia occur each year. The overall case mortality for bacteremia is about 20% but may be as high as 60% among elderly patients[10]. The incidence of pneumococcal disease is estimated to more than 35,000 cases and more than 4,200 deaths from invasive pneumococcal disease (bacteremia and meningitis) in the United States in 2011[2,12]. In Europe, the overall annual incidence of community acquired pneumonia (CAP) in adults ranged between 1.07 to 1.2 per 1000 person-years[24] (Figure 2). Interestingly, the majority of these cases concern adults with indication for vaccination against *Str. pneumoniae*. A number of clinical conditions have been identified to increase the risk for IPD development[12-15]. Patients with decreased immune function, including hematologic cancer and HIV infection or asplenia - functional or anatomic present a higher risk. More specifically, the rate of IPD for adults aged 18-64 years with hematologic cancer in 2010 was 186 per 100,000, and for individuals with human immunodeficiency virus (HIV) the rate was 173 per 100,000[12]. Furthermore, it has been shown that patients with asplenia developing bacteremia experience a fulminant clinical course. Chronic diseases, such as heart failure, pulmonary diseases, including asthma and COPD, liver or renal disease consist of risk factors for IPD development. Cigarette smoking, cerebrospinal fluid (CSF) leak and cochlear implant increase as well the risk of IPD[2] (Figure 3).



The overall annual incidence of CAP: 1,07 (1,04-1,23)/1000 person-years.
Men: 1,22 (1,18-1,26)/1000 person-years, Women: 0,93 (0,89-0,96)/1000 person-years.
Torres A, et al. Thorax. 2013;68:1057-65.

FIGURE 2. Incidence of Community Acquired Pneumonia (CAP) in Europe in patients >15 years old and major risk factors. Data fromanalysis of 60 studies.

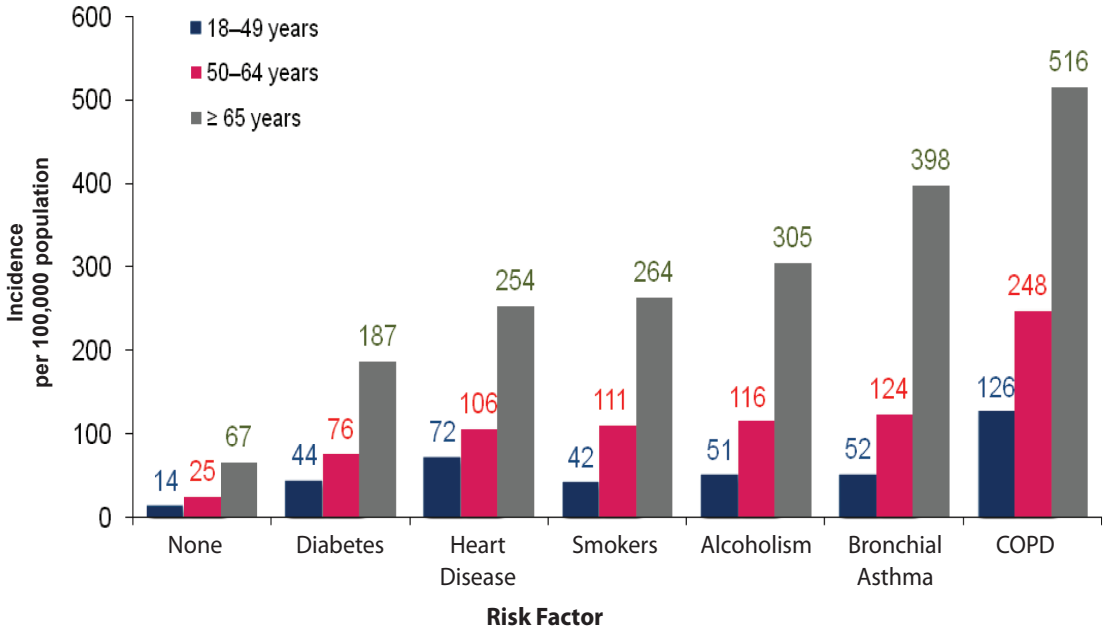


FIGURE 3. Main Risk factors for the appearance of Community Acquired Pneumonia (CAP)

IPD: CLINICAL FEATURES AND SYMPTOMS

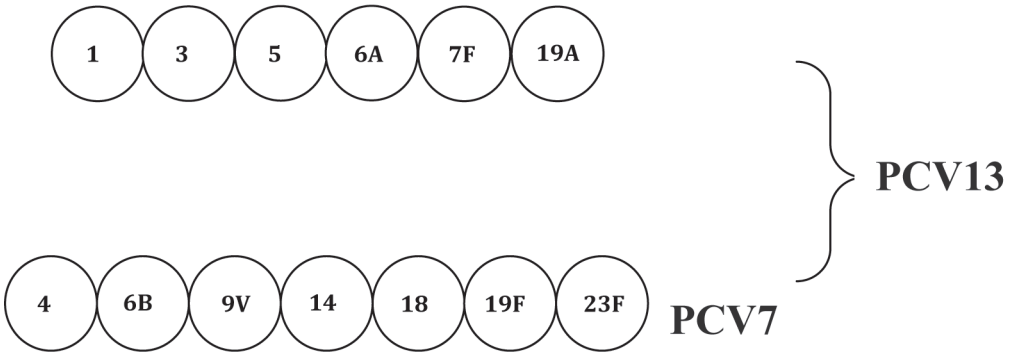
Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults. The incubation period is short, about 1 to 3 days. The nasopharynx consists of the reservoir of pneumococci, while they are transmitted by direct person-to-person contact via respiratory droplets. Infections by *Str. pneumoniae* are more commonly observed during the winter and in early spring. Symptoms generally include an abrupt onset of fever and chills or rigors. Classically chills or rigors are common. Other not specific symptoms of pneumonia could be present, including pleuritic chest pain, productive cough, dyspnea, tachypnea,hypoxia, tachycardia, malaise, and weakness. Nausea, vomiting, and headaches occur less frequently. The definitive diagnosis of IPD is based on isolation of *Str. pneumoniae* from blood or other normally sterile body sites. So far, a variety of tests have been developed, including tests that are available to detect capsular polysaccharide antigen in body fluids. A positive Gram stain with predominance of gram-positive diplococci could be suggestive of infection by *Str. pneumoniae*, however the interpretation of the stained sputum specimens may need special attention due to the presence of normal nasopharyngeal bacteria. Thus, there have been introduced suggested criteria for obtaining a diagnosis of pneumococcal pneumonia using gram-stained sputum, including more than 25 white blood cells and less than 10 epithelial cells per high-power field[10]. The urinary antigen test based on an immunochromatographic membrane technique has been widely used lately for the detection of the C-polysaccharide antigen of *Streptococcus pneumoniae (Pneumococcus* C-polysaccharide- PnC) as a cause of community-acquired pneumonia. Rapid and simple in use, it presents a coherent specificity in adults. Importantly, it is available for detecting pneumococcal pneumonia even after antibiotic therapy has been initiated[10].

IPD: PREVENTION

The prevention against IPD is achieved by vaccines against *Streptococcus pneumoniae*. The initial efforts for effective pneumococcal vaccines began as early as 1911. However, the introduction of penicillin in the 1940s resulted in a reduced interest in pneumococcal vaccination. However, the observation that many patients died despite antibiotic treatment emerged the issue and by the late 1960s, the idea of a polyvalent pneumococcal vaccine emerged again. In 1977, the first pneumococcal vaccine was licensed in the United States and in 2000 was the turn of the first conjugate pneumococcal vaccine. Two types of vaccines are available today the Pneumococcal Polysaccharide Vaccine (PPSV23) and the Conjugate Vaccine (PCV13) which replaced the previous pneumonococ-

cus conjugated vaccine (PCV7) (Figure 4). The first one contains purified capsular polysaccharide antigen from pneumococcal bacteria,and 23 types of pneumococcal bacteria, accounting for 90% of serotypes provoking IPD. PPSV23stimulates B cells to produce antibodies resulting in a T cell independent immune response[16,17] (Figure 5). However, it has been shown from different studies that PPSV23 provides a short-lasting immune response, with no booster effect and has limited efficacy in immunocompromised patients (Table 1)[2].

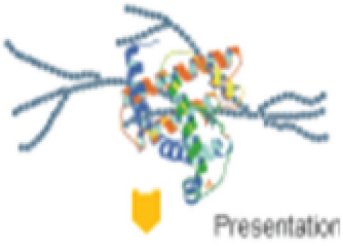
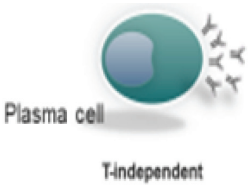
Concerning the pneumococcal conjugate vaccine, the first (PCV7) was licensed in the United States in 2000, containing purified capsular polysaccharide of seven serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and



PCV13: 13-valent pneumococcal conjugate vaccine,
PCV7: 7-valent pneumococcal conjugate vaccine.

FIGURE 4. Comparison of contained serotypes of in PCV7 and PCV13.

FIGURE 5. Differences betweenPPSV23 and PCV13.

PPSV23		PCV13	
Contain polysaccharide antigens		Contain polysaccharide antigens covalently linked to a carrier protein	
Stimulate B cells to produce antibodies		Stimulate T cells to help B cells produce antibodies and generate immune memory	
T cell-*independent* immune response		T cell-*dependent* immune response	

PPSV23: 13-valent pneumococcal conjugate vaccine, PPSV23: 23-valent pneumococcal polysaccharide vaccine.

6B) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. PCV type stimulated T cells to allow B cells to produce antibodies and to generate immune memory with a T cell-dependent immune response[16,17]. It has been generally shown that PCV type transform T-cell independent antigens into T-cell dependent antigens, providing higher affinity to IgG antibodies[2]. In 2010 a 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in the United States. It contains the 7 serotypes of *S. pneumoniae* as PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A, also conjugated to CRM197.The use of PCV7 had a great impact on the reduction of the incidence of IPD in children, as it was observed a 99% decrease caused by the vaccine serotypes, as well as by serotype 6A due to cross-reaction[2,12]. Beforethe introduction of PCV13 had suggested that approximately 61% of invasive pneumococcal disease cases among children younger than 5 years were attributable to the serotypes included in PCV13, with serotype 19A accounting for 43% of cases, while the PCV7 serotypes had caused less than 2% of cases[12].

In December 2011 the Food and Drug Administration (FDA), based on non-inferior immunogenicity compared to PPSV23, approved PCV13 as a single dose for the prevention of CAP and IPD caused by vaccine serotypes of *S. pneumoniae*in persons 50 years of age and older. More specifically, in a randomized, modified double-blindtrial which compared a single dose of (PCV13) with (PPSV23) in 831 pneumococcal vaccine naive adults 60-64 years of age, PCV13 met the primary endpoint of non-inferior immune response for all shared serotypes and concerning the secondary endpoint PCV13 was demonstrated to result in statistically significantly greater immune responses for 8 of 12 shared serotypes[20]. Similar results were also described for adults aged more than 70 years old[21]. During 2008- 2013, a randomized placebo-controlled trial (CAPiTA trial) in the Netherlands enrolled 85,000 adults older than 65 years in order to evaluate PCV13 in preventing pneumococcal pneumonia[4]. Interestingly, it was shown that the efficacy of PCV 13 against vaccine-type non- bacteremic pneumococcal pneumonia in adults older than 65 years was approximately 45.6%, while against vaccine-type pneumonia caused by *Str. pneumoniae* around 45.6% and against vaccine-type invasive pneumococcal disease (IPD) 75%. Moreover, in an observational cohort study, conducted in England and Wales 4 years after the introduction of PCV13 observed 32% decrease in incidence of IPD compared with the pre-PCV13 baseline[18]. The aforementioned results were attributed to a 86% reduction of the serotypes covered by PCV7 and a 69% reduction of the additional six serotypes covered by PCV13[18].

VACCINATION PROGRAMS

Pneumococcal Conjugate Vaccine (PCV13)

In December 2011, PCV13 was licensed for use in adults older than 50 years old for the prevention of IPD. However, the recommendations for routine use among all adults aged more than 50 years old will be reevaluated in 2018 and revised as needed. Until now, the recommendations of Advisory Committee Practices (ACIP)of USA are as followed. Adults 65 years of age or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive initially a dose of PCV13. In high risk adults for the appearance of IPD, aged more than 65 years old (chronic diseases, malignancies etc) one dose of PPSV23 should be given 6-12 months after the dose of PCV13. Regarding PCV13-naïve adults aged more than 65 years, who have previously received one or more doses of PPSV23 a dose of PCV13 should be received 6 to 12 months after PPSV23 (Table 2). Immunogenicity and safety of the sequential vaccination protocols was studied by Greenberg RN and colleagues and concluded that an initial use of PPSV diminished the response to a subsequent dose of PCV13 compared to PCV13 alone, whilst an initial use of PCV13 enhanced the response to a subsequent dose of PPSV compared to PPSV alone[23]. The two vaccines should not be administered simultaneously on the same day and the minimum suggested acceptable interval between PCV13 and PPSV23 is 8 weeks. Generally, PPSV23 should be given 6-12 months after the dose of PCV13.

In addition, in 2012, ACIP recommended vaccination of adults 19 years and older with specific risk factors, including functional or anatomic asplenia - sickle cell disease, splenectomy, HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, other conditions associated with immunosuppression, such as organ or bone marrow transplantation, or immunosuppressive chemotherapy and long-term corticosteroids, CSF leak or cochlear implants (Table 3, 4). Adults with these specific risk factors should initially receive a dose of PCV13, followed by a dose of PPSV23 after 6 to 12 months. Revaccination with PPSV23 is recommended 5 years after the first PPSV23 dose (Table 3)[2]. Minor solicited adverse events there have been observed, including local

TABLE 2. Differences between the two available vaccines against *Str. pneumoniae*

Caracteristics	PPSV23	PCV13
Activates B-cells - no immune memory	●	
Activates B-cells and T-cells - immune memory		●
Short-lasting immune response, revaccination needed after 5 years	●	
No need for repetitive dose		●
Transforms T-cell independent antigens into T-cell dependent antigens		●
Higher affinity IgG antibodies		●
No reduction of nasopharyngeal carriage	●	
Limited efficacy in immunocompromised patients	●	
Proven activity in immunocompromised patients		●
Broad coverage (23 out of 94 serotypes)	●	
Narrowcoverage (13 out of 94 serotypes)		●

PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine.

TABLE 3. ACIP recommendations for vaccination against IPD in adults ≥65 years old.

Patients	Vaccination history	Initial	Following by[1,2]
Persons > 65 years old	Without previous vaccination history*	A single dose of PCV13	A dose of PPSV23 administered after 6-12 months after PCV13
	Previously received one or more doses of PPSV23	A dose of PCV13 at least one year after the last PPSV23 dose	
	Previously received PPSV23 before the age of 65 years old	A dose of PCV13 at least one year after the last PPSV23 dose	A dose of PPSV23 after five years from the most recent dose of PPSV23

ACIP: Advisory Committee on Immunization Practices, PCV13: 13-valent pneumococcal conjugate vaccine, PPSV23: 23-valent pneumococcal polysaccharide vaccine.
*without previous vaccination history or whose previous vaccination history is unknown
[1,2] The administration of additional doses is decided from the attending physician based on the risk factors of each patient, whilst the aim is to broaden the coverage against more serotypes of *Str. pneumoniae*.

TABLE 4. ACIP recommendations for IPD vaccination in immunosuppressed adults >19 years old

Patients	Vaccination history	Initial	Followed by[1,2]
Immunosuppressed adults >19 years old	Without previous vaccination history*	1 dose PCV13	1 dose PPSV23 (≥8 weeks after administration of PCV13)
	Previously received PPSV23	A dose of PCV13 at least one year after the last PPSV23 dose	A dose of PPSV23 (≥8 weeks after administration of PCV13 and not sooner than five years from the most recent dose of PPSV23

ACIP: Advisory Committee on Immunization Practices, PCV13: 13-valent pneumococcal conjugate vaccine, PPSV23: 23-valent pneumococcal polysaccharide vaccine.
*without previous vaccination history or whose previous vaccination history is unknown
[1,2]The administration of additional doses is decided from the attending physician based on the risk factors of each patient, whilst the aim is to broaden the coverage against more serotypes of *Str. pneumoniae*.

reactions, such as pain, redness, swelling and limitation of the arm movement, as well as systemic events - fever, diarrhea, fatigue, headache, vomiting, decreased appetite, rash and muscle/joint pain (Table 6) while any serious adverse events and deaths did not differ significantly between the vaccine and the control group (Table 6)[4].

PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPSV23)

PPSV23 recommendations suggest the routine vaccination of all adults 65 years of age and older and their revaccination after 5 years, as well as persons more than 2 years old with chronic diseases (cardiovascular disease, pulmonary disease, diabetes, alcoholism, chronic liver disease, cirrhosis, splenic dysfunction or absence, Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, cerebrospinal fluid leak, or a cochlear implant asymptomatic or symptomatic HIV infection, organ transplantation, chemotherapy or high-dose corticosteroid therapy for longer than 14 days) (Table 3)[2]. Pneumococcal vaccine is also suggested for persons living in specific environments or social settings with an identified increased risk of pneumococcal disease, such as certain Native American (i.e., Alaska Native, Navajo, and Apache) populations (Table 5). Moreover, in 2010 ACIP added asthma and cigarette smoking to the list of indications for PPSV23 vaccination due to increased risk of IPD[2].

Regarding the suggested revaccination with PPSV23, immunocompetent adults aged 19 through 64 years old with chronic heart disease, pulmonary disease -including asthma, liver disease, alcoholism, CSF leaks, cochlear implants, or those who smoke cigarettes should receive one dose of PPSV23 before the age of 65 years. A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for those aged 19-64 years with functional or anatomic asplenia – including sickle cell disease or splenectomy, as well as immunocompromised adults with medical conditions, such as HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression, such as organ or bone marrow transplantation and those receiving immunosuppressive treatment, including chemotherapy and long-term corticosteroids[2]. The 30%–50% of vaccinated individuals report local reactions, such as pain, swelling, or erythema at the site of injection, symptoms that usually persist for less than 48 hours (Table 7). These aforementioned local reactions are reported more frequently following the second dose of PPSV23 than following the first dose. Moderate systemic reactions, including fever and myalgia have been reported in less than 1% of the vaccinees, while more severe systemic adverse reactions are generally rare.[2]

Regarding daily clinical practice, in cases where elective

TABLE 5. PCV13 vaccination in highrisk adults >19 years old

Anatomic asplenia (functional or anatomic)
Immunocompromising conditions (HIV infection, immunosuppression, organ or bone marrow transplantation, immunosuppressive chemotherapy, long-term corticosteroids Cochlear implant
Cerebrospinal fluid leak
Hematological Diseases (leukemia, lymphoma, Hodgkin disease, multiple myeloma), generalized malignancy
Chronic illness (Chronic renal failure, nephrotic syndrome, cardiovascular disease, pulmonary disease, diabetes, chronic liver disease)
Bronchial Asthma
Cigarette smoking

PCV13: 13-valent pneumococcal conjugate vaccine

TABLE 6. PPSV23 Recommendations

A. Adults 65 years and older
B. Persons 2 years and older with
Chronic illness
Anatomic or functional asplenia
Immunocompromised (chemotherapy, steroids)
HIV infection
Environments or settings with increased risk
Cochlear implant
CSF leak

PPSV23: 23-valent pneumococcal polysaccharide vaccine.

TABLE 7. Adverse Events of Pneumococcal Vaccines

	PPSV23	PCV13
Local reactions	30%–50%	5%–49%
Moderate systemic reactions (fever and myalgia)	<1%	24%–35%
Severe adverse reactions	Rare	8%

PCV13: 13-valent pneumococcal conjugate vaccine, PPSV23: 23-valent pneumococcal polysaccharide vaccine.

splenectomy or cochlear implant is being considered, the vaccine should be given at least 2 weeks before[2]. In the same way, a 2-week interval is recommended between vaccination and initiation of chemotherapy or other immunosuppressive therapy, if possible. Both, pneumococcal and influenza vaccines can be given at the same time but at different anatomical sites. PCV13 should never be performed during the same visit with PPSV23. There are no guidelines supporting the vaccination with PCV13 or PPSV23 in pregnant women.

In conclusion, prevention against IPD is achieved by the use of the two available vaccines against *Streptococcus pneumoniae*, the polysaccharide pneumonococcus vaccine (PPSV23) one and the pneumonococcus conjugated vaccine (PCV13). The knowledge of immunogenicity and vaccine efficacy, as well as the minor adverse effects and the recommended vaccination programs constitute a critical issue for modern pulmonologists.

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