Consensus on pneumococcal vaccination in adults with underlying pathologies[◊, Δ]

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ABSTRACT

Invasive pneumococcal disease (IPD) represents an important health problem among adults with certain underlying pathologies and some diseases, especially immunosuppressed and some immunocompetent subjects, who are more susceptible to infections and present greater severity and worse evolution. Among the strategies to prevent IPD, vaccination has its place, although vaccination coverage in this group is lower than desirable. Nowadays, there are 2 vaccines available for adults. Polysacharide vaccine (PPV23), used in patients aged 2 and older since decades ago, includes a greater number of serotypes (23), but it does not generate immune memory, antibody levels decrease with time, causes an immune tolerance phenomenon, and have no effect on nasopharyngeal colonization. The conjugate vaccine (PCV13) can be used from infancy to adult age (the indication in subjects older than 18 years received approval by the European Medicines Agency in July 2013) and generates an immune response more powerful than PPV23 against most of the 13 serotypes included in it. The 16 Scientific Societies most directly related to groups of risk of presenting IPD have worked in the discussion and preparation of a series of vaccine recommendations based on scientific evidence regarding anti-pneumococcal vaccination in adults with underlying pathologies and conditions detailed in this document. This is a "live" document that will keep being updated as new scientific evidence becomes available.

KEYWORDS, Invasive Pneumococcal Disease, pneumococcus, *S. pneumoniae*, vaccination, adult, underlying pathology, risk group, consensus.

10 KEY POINTS

1. Pneumococcal infection and more specifically invasive pneumococcal disease (IPD) is an important cause of morbidity and mortality worldwide.
2. IPD may present in different clinical forms, and, among them, bacteremic pneumonia is the most frequently reported. Certain underlying concomitant diseases and conditions increase the risk of IPD and its evolution.
3. Prevention of pneumococcal infection through vaccination can positively contribute to decreasing the resistances of *Streptococcus pneumoniae* to antibiotics that had been observed before the introduction of conjugate vaccine for children.
4. Polysaccharide vaccine (PPV23), used in subjects older than 2 years since decades ago, includes a greater number of serotypes (23), but it does not generate immune memory, antibody levels decrease with time, causes an immune tolerance phenomenon, have no effect on nasopharyngeal colonization and has not shown vaccine effectiveness in these risk groups in the United Kingdom despite a 75% of vaccination coverage.

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ΔThe recommendations in this document are based on data and results from studies available at the time of publication. The document will, eventually, be updated according to new scientific evidences available. Such updates will previously be approved By all the signing Scientific Societies and published in their webpages indicating in the footnote the number of the version and the date of the update.

5. Conjugate vaccine (PCV13) may be used in any age from the first 6 weeks after birth, generates immune memory and a more powerful immune response than the polysaccharide vaccine.
6. Although it would be desirable to have available a greater number of studies on the protective effects of both vaccines for the pneumococcal infection in adults with underlying pathologies, a clear benefit is expected, especially with the conjugate vaccine (PCV13).
7. Probably, the most cost-effective measure in the nearby countries in order to prevent morbidity and mortality associated with pneumococcal infection in adults with underlying pathologies may be that obtained by vaccinating children (indirect protection). In the absence of systematic vaccination for children, PCV13 seems to be justified in subjects with immunodeficiencies or certain other underlying pathologies.
8. Among the risk groups, subjects with functional or anatomic asplenia, CSF fistula, cochlear implants and immunosuppressed subjects were considered eligible for vaccination: Hodgkin's disease, leukemia, lymphoma, multiple myeloma, stage 4-5 chronic kidney disease and stage 3 with increased risk (nephrotic syndrome, diabetes mellitus or treatment with immunosuppressives), solid organ transplant or hematopoietic cells transplant, chemotherapy or immunosuppressive treatment, HIV infection, autoimmune inflammatory rheumatologic disease and inflammatory bowel disease (including Crohn's disease and ulcerous colitis).
9. Immunocompetent subjects with other underlying pathologies or risk factors were also considered as eligible for vaccination. Such associated diseases were: Chronic respiratory disease (including COPD, severe asthma and diffuse pulmonary interstitial pathology), chronic liver disease (including cirrhosis), chronic cardiovascular disease (includes coronary heart disease, congestive heart failure and stroke), diabetes mellitus in treatment with OAD or insulin-dependent diabetics, smoking and alcohol abuse.
10. The 16 Scientific Societies who signed this Consensus consider that adults with underlying pathologies included in keypoints 8 and 9 shall be vaccinated against pneumococcus and receive, preferably, at least 1 dose of PCV13, which will always be administered before PPV23 in those cases where revaccination is indicated.

OBJECTIVE/RATIONALE

As of June 2010, the conjugate vaccine against 13 serotypes of *S. pneumoniae* is available in Spain. Its indication to prevent invasive pneumococcal disease (IPD) was extended to adults aged 50 years or more by the European Medicines Agency in October 2011[1]. On May 30th, 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) disclosed its positive opinion regarding the extension of the indication to any adult aged 18 years or more[2]. This was then followed by the EMA's final approval on July 9th, 2013[3].

During 2012, the Autonomous Community of Madrid in July[4]; Galicia[5] and Murcia[6], as well as the *Sociedad Española de Medicina Preventiva, Salud Pública e Higiene* (Spanish Society of Preventive Medicine, Public Health and Hygiene)[7] in September; and the *Grupo de trabajo del Área de tabaquismo de la Sociedad Española de Neumología y Cirugía Torácica* (Tobacco Use Working Group of the Spanish Society of Pneumology and Thoracic Surgery)[8] in December, and the Basque Country in March 2013[9], published an update for their guidelines on anti-pneumococcal vaccine in adults for medical indications, or subjects pertaining to risk groups, for which the conjugate vaccine would provide an important benefit.

Given the wide range of medical conditions favoring greater IPD incidence, as well as the variable response to the different anti-pneumococcal vaccines available, it is appropriate and necessary that all the medical specialties involved, through their corresponding scientific societies as primary organs for expression, collaborate to assess and discuss current evidence and combine all the guidelines regarding the available vaccines into one unique Consensus document.

This document does not attempt to offer an exhaustive review exercise, since there is a vast literature available for this area. The present document aims to expose and simplify, in a clear manner, the basis for final recommendations created by the group regarding anti-pneumococcal vaccines in adults with underlying diseases. This is also a "live" document, since it can be updated when new scientific evidence becomes available, and is accessible on the Internet through the corresponding web pages of the participating scientific societies.

PNEUMOCOCCAL DISEASE AS A HEALTH PROBLEM

Epidemiology, burden of the disease and mortality

S. pneumoniae constitutes an important cause of morbidity and mortality worldwide[10]. According to WHO estimations, it is responsible for 1.6 million deaths every year. It is the disease, preventable through vaccines, that causes more deaths[10], with younger children and older adults being most affected[11]. In Spain, where *S. pneumoniae* is the pathogenic agent most frequently identified in community-acquired pneumonia (CAP), responsible for up to 63.7% of deaths in certain case series[12]; for the 2003-2007 period, a total of 75,932 deaths by CAP were registered in adults aged 50 years or more[13]. Mortality associated to pneumococcal pneumonia oscillates between <1% in young adults and 10-30% in bacteremic pneumonia in the elderly[14]. In Spain, a retrospective study of 263 cases over 10 years in a hospital of Madrid estimated a mortality of 12.5%[15]. Among the prospective studies about bacteremic pneumonia and non-bacteremic pneumonia, one study in adults, with 309 cases of pneumococcal pneumonia, found a mortality rate of 7.4%[16]. Another study that included 11,240 subjects aged 65 years or more, from different locations in Spain, found a mortality rate of 13%[17].

Invasive pneumococcal disease (IPD) represents the most severe pneumococcal disease and is defined as the presence of *S. pneumoniae* in the blood, cerebrospinal fluid (CSF) or other fluids that are normally sterile[18]. IPD by definition does not include, therefore, pneumonia, unless it is accompanied by bacteremia. The highest incidence rates for IPD take place in the extremes of age groups[19]. According to data in Spain (2007-2009), the average incidence rate (IR) per year in children younger than 2 years is 49.79 cases/10^5 inhabitants and 20.76 cases/10^5 inhabitants older than 65 years[20].

IPD can present in several clinical forms, with bacteremic pneumonia the most frequently reported presentation. In the adult, 60-87% of all the pneumococcal bacteremia cases are attributable to pneumonia[21]. In Spain, according to a multicenter, prospective, hospital-based surveillance study of IPD (ODIN study) for the 2010-2012 period, of the 436 patients included, 156 (35.8%) presented an uncomplicated pneumonia, 147 (33.7%) a complicated pneumonia (defined as pneumonia with pleural effusion, and/or empyema, and/or multilobar involvement), 43 (9.9%) a meningitis, 31 (7.1%) a bacteremia without focus, 25 (5.7%) severe sepsis, 15 (3.4%) peritonitis and other clinical forms 31 patients (7.1%). Even though the average age was 62.7 years, more than 50% of the patients included were older than 65 years. Regarding the acquisition site, 78% were community-acquired, 15.3% were associated with health care and 6.7% were nosocomial[22].

One of the main clinical presentations caused by *S. pneumoniae* is pneumonia, especially the community-acquired pneumonia (CAP). But its microbiological documentation is not always possible, and only a small percentage produces bacteremia. Therefore, not all cases can be considered to be IPD. CAP incidence in Spain, in subjects older than 65 years is estimated to be 14 cases per 100 person-years (95% CI; 12.7-15.3) and increases with age (29.4 cases per 100 person-years in subjects older than 85 years)[17]. Furthermore, it represents an important burden, since up to 75% of the cases require hospital admittance[17]. In Spain, according to national data of the Basic Minimum Data Set (BMDS), for the CAP, the annual incidence rate for the hospitalizations during the 2003-2007 period was of 6.27 cases/1000 inhabitants aged 50 years or older, and of 10.29 cases/1000 inhabitants aged 65 years or older, with no differences in incidence, mortality or lethality rates within the periods[13]. Variables significantly associated with hospitalization due to CAP ($p<0.002$), according to a study performed in Badalona (Barcelona, Spain), for the period 2008-2009, were chronic liver disease (OR 5.9), ictus (OR 5.9), dementia (OR 3.5), COPD (OR 2.9) and diabetes mellitus (OR 1.9). In this study, the most frequently identified pathogen was *S. pneumoniae* (57.5%; 34.7% in ambulatory patients and 71.9% in patients admitted to the hospital, $p<0.001$)[23].

Underlying pathologies and condition as risk factors

Apart from the age, certain underlying concomitant diseases and conditions have been described as increasing the risk of invasive pneumococcal disease and its evolution. Among them, those medical conditions involving an immune deficiency state, or a disorder of local defenses of the target organ, such as the chronic, kidney, liver, respiratory and cardiovascular disease stand out. Likewise, HIV-infected patients, patients waiting for a solid organ transplant and patients with a solid organ transplant and/or hematopoietic stem cell transplantation, patients on chemotherapy due to a solid or malignant hematological disease; patients with autoimmune disease treated with corticosteroids, immunosuppressants or biologicals; diabetics; with cerebrospinal fluid leaks, cochlear implants and patients with anatomic or functional asplenia.

A review of the clinical histories of more than 22,000 patients hospitalized due to IPD in England and Wales in 2008/2009 shows that the main risk factors for suffering IPD in the age group between 16 and 64 years are: HIV infection, chronic liver disease, chronic respiratory disease and immune suppression, compared to the healthy subject in which the incidence rate was estimated to be 5.2 cases per 10^5 inhabitants[26].

Table 1 **Odds Ratio (OR) and incidence rate (IR) for 10^5 inhabitants for suffering IPD according by age according to underlying pathologies in England and Wales. Adapted from Van Hoek et al.[26]**

	2-15 years		16-64 years		≥ 65 years	
	IR	OR	IR	OR	IR	OR
Healthy	3.9	1	5.2	1	17.9	1
Functional or anatomic asplenia	19	4.7	12	2.3	13	0.7
Chronic respiratory disease	50	12.7	91	16.8	91	5.1
Chronic heart disease	16	4.1	36	6.9	54	3
Chronic kidney disease	46	11.7	34	6.5	16	0.9
Chronic liver disease	117	29.6	172	33.3	129	7.2
Diabetes	15	3.8	24	4.6	41	2.3
Immunosuppression	162	41	88	17.1	209	11.7
HIV infection	398	100	316	61.2	95	5.3

Regarding the subjects aged 65 years or older, a greater risk corresponded to those who were immunosuppressed (table 1)[26].

In the USA, Kyaw et al.[27] also estimated the IPD incidence in adults according to the underlying disease based on the revision of surveillance data of IPD of the *Active Bacterial Core Surveillance* (ABC) of the 1999-2000 period. The estimated rate in healthy adults was of 8.8 cases per 10^5 inhabitants versus 503.1 cases per 10^5 inhabitants for the hematological cancer. The factors suggesting the greatest risk, without adjusting for OR, were HIV/AIDS infection (which was the main factor after adjusting for OR), patients with solid organ neoplasia, alcohol consumption, chronic heart disease, chronic respiratory disease and, finally, diabetes mellitus (table 2)[27]. Patients infected with HIV seem to present a special risk for suffering IPD, which is associated with the degree of immunosuppression, with being older than 64, and with having not received previous antiretroviral drugs[28]. In 11% of the patients infected with HIV, recurrent IPD is described[29].

Patients receiving hematopoietic stem cell transplantations (HSCT) constitute one of the groups at a greater risk for IPD. IPD global incidence in allogeneic HSCT is of 8.23 cases/1000 transplantations, achieving 20.8/1000 cases in patients with chronic graft-versus-host-disease (GVHD)[30]. In patients receiving autologous HSCT, the incidence is lower, 3.8 cases/1000 transplantations, but it is clearly higher than that found in the immunosuppressed population[30].

Alcohol abuse has been clearly associated with pneumococcal pneumonia. Such association is also dose-dependant[31] and favors more severe clinical presentations. In a Spanish study, it has even been shown as an independent risk factor for ICU admittance (OR 1.9; p=0.01)[32,33]. Its relationship with IPD has also been demonstrated. In the ODIN study, 11.5% of the total of adult patients with IPD confirmed in 9 Spanish hospitals from 2010 to 2012 presented comorbidity of alcohol abuse (23.9% in the group aged 50 to 64 years)[34]. In a study that lasted 10 years with around 19,000 patients, a 30% mortality rate attributable to IPD in alcoholic patients was found. Non-alcohol consumers showed a 17% mortality rate[35]. There are several physiopathological mechanisms suggested for this association, but the principal, and most known, is the functional alteration of alveolar macrophagues[32,36]. Others, such as a disorder in the function of polymorphonuclear leukocytes, B lymphocytes and antibodies neutralizing endotoxins favoring infection evolution and sepsis[37-39] can be added. On the other hand, an alteration of the present immunity in alcohol abuse disorders as an independent factor, is commonly associated to other factors contributing to increasing the risk of infection, such as malnutrition, liver disease, poor dental hygiene or active smoking[39,40].

A greater risk of bacterial infections, of IPD and CAP, has been described among smokers, mainly due to three factors: the reduction of pulmonary and nasal clearance, the increase in bacterial adherence and changes in immune responses, innate and adaptive immunity, operating in the smoking group[41-44]. The increase in the risk of severe pneumococcal pneumonia after exposure to tobacco due to an alteration in the *S. pneumoniae* clearance by alveolar macrofagues and has been proven in animal models. Nuorti et al. analyzed all immunocompetent subjects who had suffered IPD in different American and Canadian cities. A total of 228 subjects were identified and 301 subjects were used as controls. The authors found that IPD was significantly associated with smoking with an OR of 4.1 (95% CI 2.4-7.3) (the strongest association of an independent risk factor and an attributable risk of 51%)[45]. Furthermore, there was a positive association dose/response, not only regarding the amount of packages/year consumed, but also regarding the time of smoking cessation. In Spain, Almirall et al.[46], in a 2008 study with a population including more than 800,000 subjects, after the multivariate analysis, smoking was identified as CAP risk factor with an OR of 1.48 (95% IC 1.14-1.86) in subjects smoking more than 180 packages/year. Previously, Almirall et al., had already described an association dose/response between smoking and the likelihood of developing CAP, as well as the reduction of the risk after terminating smoking[47]. Other studies have found it as an independent risk factor for suffering a severe CAP of pneumococcal etiology with an OR of 2.11 (95% IC 1.02-4.34, p=0.04) of presenting septic shock[48,49]. In the population with HIV infection, smoking has been described in several studies as the principal risk

Table 2 **Odds Ratio (OR) and incidence rates (IR) per 10^5 inhabitants for suffering IPD based on underlying pathology in USA. Adapted from Kyaw et al[27]**

	IR	OR	(95% CI)	OR	(95% CI)
		Non-adjusted		Adjusted	
Healthy	8.8	1		1	
Solid tumor	300.4	32.2	7.8-132.2	22.9	11.9-44.3
Hematological tumor	503.1	52.2	7.9-345.6	38.3	15.9-92.2
Chronic heart disease	93.7	10.4	3.6-30.6	6.4	3.7-10.9
Chronic respiratory disease	62.9	6.9	1.7-28.1	5.6	3.2-9.9
Diabetes mellitus	51.4	5.8	1.6-21.0	3.4	1.8-6.4
HIV/AIDS infection	422.9	48.8	7.9-302.3	48.4	24.8-94.6
Alcohol abuse	100.4	11.5	2.2-60.8	11.4	5.9-21.9

factor for developing bacteremic pneumonia during combined antiretroviral treatment[50,51]. The intensity of the smoking habit can be quantified according to the number of cigarettes smoked a day per 20 (one package), which is multiplied by the number of years smoking and is expressed as years/package or packages/year. According to the SEPAR smoking study group, the greater IPD risk and the greater benefit of its prevention can be found in the active smokers group with a burden of 15 or more years/package without comorbidity, the group of ex-smokers with a burden of at least 20 years/package who have been at least 10 years without smoking, and any other smoker regardless of age, intensity and/or disease burden, who suffers respiratory diseases[8].

Apart from COPD, asthma can be found among the chronic respiratory diseases that seem to act as risk factors. In a Swedish case-control study with 4,058 cases of IPD and 40,353 controls, IPD's OR was estimated for subjects with different respiratory diseases. In subjects aged 18-59 years, asthma was associated to IPD with an OR of 4.9 (95% CI 3.0-7.8) (table 3)[52]. However, the difficulties presented by asthma are its very variable affectation degrees. Talbot et al. estimated an IPD risk based on a case control study that included 6,985 subjects (635 cases and 6,350 controls) with asthma of any severity, the OR associated to IPD varied from 2.3 (95% CI 1.4-4) for subjects aged 2-4 years and 18-49 years, to 4 (95% CI 1.5-10.7) for subjects aged 5-17 years[53]. However, the high risk group (one or more hospitalizations or visits to the ER; the use of rescue therapy or oral corticoids for long time periods or the prescription of 3 or more beta-agonists in the previous year) is the most likely to suffer IPD, whose yearly incidence of IPD in patients with no other risk factor was of 4.2/10,000. The incidence for the moderate asthma was 2.3/10,000 (incidence of 1.2/10,000 in patients without asthma). In a Finnish study with at least 1,300 patients and 13,000 controls of 18 and 49 years of age, from 1995 to 2002, a very high risk of IPD was found in asthmatic patients, both those at high risk (OR 12.3; 95% CI 5.4-28.0) and those at low risk who were defined as those who received drugs but required no hospitalization in the previous 12 months (OR 2.8; 95% CI 2.1-3.6)[54].

Patients with chronic kidney disease (CKD) have a certain degree of immunosuppression and an increased risk of being admitted due to infections, as well as a longer hospital stay than subjects with normal kidney function.

We define stage 4 and 5 CKD as the situation where the patient maintains an estimated glomerular filtration rate inferior to 30 ml/min/1.73m^2 (between 30-59 ml/min/1.73m^2 for the stage 3)[55]. eGFR measurements are based on the measure of standardized serum creatinine and the application of the CKD-EPI formula[55].

The most relevant risk factors for CKD are the presence of associated proteinuria and the progression in the eGFR fall. It is estimated that 6.5% of Spanish subjects suffer CKD3, 0.27% CKD4 and 0.03% CKD5[56]. In USA, CKD patients have a risk 3 times higher for suffering pneumonia and 4 times higher for bacteremia/sepsis than individuals with normal kidney function. For this reason, KDIGO (Kidney Disease Initiative Global Outcomes) world guides published in 2013, recommend that all adults with stage 4-5 CKD and those with stage 3 CKD with an increase risk (nephrotic syndrome, or DM, or immunosuppressant treatment) should receive the pneumococcal vaccine, unless it is specifically contraindicated in each case[57]. We know that the vaccine response in these patients is reduced, and that the loss of vaccine titers is faster, which should be taken into account for re-vaccinations[57].

The group at the Public Health Department of the University of Oxford studied retrospectively –starting from a cross-sectional data base of clinical pictures in Oxford (1963-2008) and the English national hospital statistics (1999-2008)- the risk of hospitalization due to IPD in patients with diseases mediated by the immune system compared to control cohorts[58]. Risk increases were observed for systemic lupus erythematous [RR: 5.0 (95% CI 4.6-5.4)], polyarteritis nodosa [RR: 5.0 (95% CI 4.0-6.0)], autoimmune hemolytic anemia [RR: 4.9 (95% CI 4.4-5.3)], scleroderma [RR: 4.2 (95% CI 3.8-4.7)], Addison's disease [RR: 3.8 (95% CI 3.4-4.2)], diabetes mellitus [RR: 3.7 (95% CI 3.4-4.1)], multiple sclerosis [RR: 3.7 (95% CI 3.5-3.8)], primary biliary cirrhosis [RR: 3.3 (95% CI 2.9-3.7)], Sjögren´s syndrome [RR: 3.2 (95% CI 2.9-3.5)], rheumatoid arthritis [RR: 2.5 (95% CI 2.4-2.5)], Chrohn's disease [RR: 2.2 (95% CI 2.1-2.3)], pernicious anemia [RR: 1.7 (95% CI 1.6-1.8)], and myxedema [RR: 1,6 (IC95% 1,6-1,6)[58]. The pneumococcal infection risk is increased in autoimmune diseases, even in patients not submitted to immunosuppressive treatment[58,59]. Certain studies point out a previous pneumococcal pneumonia antecedent among patients with pneumococcal infection[34,60], and events.

The WHO included it among their vaccine indications with PPV23 in 1999, although it is not included in their last recommendations or the ACIP's USA recommendations[24,61,62]. In Spain, the Basque Country and Murcia regions have included the antecedents of confirmed previous IPD in their funding conditions for

Table 3 **Odds Ratio (OR) per age based on respiratory disease. Adapted from Inghammar et al.[52]**

	18-59 years		60-79 years		≥ 80 years	
Respiratory disease	OR	95% CI	OR	95% CI	OR	95% CI
COPD	10.3	5.8-18	6.3	5.1-7.8	4.0	3.0-4.8
Asthma	4.9	3.0-7.8	1.9	1.3-2.9	1.5	0.9-2.7
Pulmonary fibrosis	6.5	1.1-39.1	11.6	3.9-34.4	4.4	1.5-12.6

PCV13[6,9]. A confusion factor may exist between the association of previous pneumonia and the subsequent IPD episode. Currently, scientific evidence does not seem to be strong enough to make such recommendations in a systematic manner. Given that this is a "live" document, any new scientific evidence will be exhaustively studied, both previous IPD and previous pneumococcal pneumonia could be recommended in future updates.

Underlying disease, apart from increasing IPD risk, may influence the type of clinical presentation and the subsequent evolution. Thus, in Spain, according to the ODIN study[63], primary bacteremia and meningitis are more frequent in those patients who suffer any type of immunosuppression (including: neoplasia; chronic renal disorder/nephrotic syndrome, solid organ or hematopoietic stem cell transplantation, immunosuppressant or chemotherapy treatment, immunodeficiency and HIV/AIDS infection) than in immunocompetent patients, with a significantly higher lethality (table 4)[63]. In a Dutch study, splenectomized patients with pneumococcal meningitis presented septic shock in 63% of the cases, versus 24% in patients with a healthy spleens (p=0.02)[64]. In Spain, the mortality rate due to IPD in splenectomized patients has been described ast 55%[65]. In HIV-infected patients, mortality in the month following the IPD episode reaches 25%, having increased in a statistically significant way from 1996 to 2007[66]. Mortality due to IPD has also shown to be greater in cirrhotic patients than in non-cirrhotic patients, with no other immunodeficiency factors, as well as in patients treated with immunomodulators[25,27].

Regarding CAP, the most frequently identified comorbidities among the 1,002 hospitalizations caused by CAP assessed for 2 weeks in Spain (January and June 2010), were:

COPD (37.4%), congestive heart disease (21.3%), diabetes mellitus (25.2%), ictus (17.9%) and dementia (16.6%). The estimated intra-hospital mortality rate in this study was 7.8%[12]. Furthermore, a Spanish study demonstrated that pneumococcal strains producing acute exacerbations of COPD in patients aged 65 or more were more resistant to antibiotics than those producing pneumonia in patients with the same age and in the same region[67]. Lastly, a greater risk of cardiovascular disease (including acute myocardial infarction or brain stroke) has been described up to 3.65 times more in patients with previous pneumococcal pneumonia and, although it has not been possible to demonstrate a protective effect due to vaccination, it is undoubtedly an area for further research given the important clinical implications that it could involve[68-71]. Generally speaking, an increased mortality risk 10 years after suffering a pneumococcal pneumonia has been described[72].

The problem of *S. pneumoniae* resistance

Although none of the currently marketed vaccines have been designed to decrease or suppress resistance to antibiotics or their prescription, it has been demonstrated that their use could achieve this in a direct or indirect way[73]. The resistance of pneumococcus is clearly related to the use of antibiotics due to the ecologic impact they have on nasopharyngeal strains[74-76]. Children and adults, since they receive more repeated cycles of antibiotics, usually carry serotypes that commonly develop resistance, mainly 6B, 9V, 14, 19F and 23F[77], in the period previous to vaccine PCV7 introduction, and representing up to 88% of the serotypes of penicillin-resistant invasive pneumococcus in the period 1998-2000 in Spain[78].

Table 4 **Distribution of patients according to underlying pathology and immune situation. Adapted from Rodríguez-Creixems M et al[63]. *p<0.001 **p<0.05 ***p<0.01**

% patients	Immunocompetent N=243	Immunosuppressed N=193
At least 1 underlying disease (%)	82.3	100
Chronic respiratory disease (%)	33	25.9
Previous pneumonia (%)	8.5	33.2*
Chronic liver disease (%)	16.5	26.4**
Diabetes mellitus (%)	21.5	17.6
Lethality	9.5	18.1**
Clinical presentation (n/%)		
Primary bacteremia	8/3.3	23/11.9**
Severe sepsis	11/4.5	14/7.3
Complicated pneumonia	89/36.6	58/30.1
Non-complicated pneumonia	90/37	66/34.2
Meningitis	30/12.3	13/6.7
Other	15/6.2	16/9.8**
Previous vaccination history with PPV23 (%)	15.6	23.3***

PCV7 vaccine effectiveness for decreasing invasive disease incidence has been directly associated with a decreased use of antibiotics, documented in the USA, Israel or France among others, with decreases of 42%, 17% or 21%, respectively[74]. This involves a lower selective pressure pushing toward the appearance or dissemination of resistant strains. In Spain; a decrease in the use of antibiotics, from 21.66 daily doses/1000 inhabitants-day in 1998 to 19.71 in 2002 (p<0.001) was described[79].

Most studies have documented, since the first introduction of PCV7 vaccine, a parallel decrease in infections caused by non-penicillin-susceptible pneumococcal strains. In USA, for example, a decrease of 81% in IPD incidence by these strains, from 1996 to 2004, in children younger than 2 and 49% in adults older than 65 was observed[80]. This decrease has also been documented with other antibiotics, such as third generation cephalosporins or macrolides[75].

In Spain, a decrease in non-penicillin-susceptible pneumococcus causing IPD was early documented to have taken place from 39.5% in 2001 to 33% to 2003 (p=0.05). Such decrease was more significant in the group aged younger than 14 years (from 60.4% to 41.2%, p=0.002)[79]. The *Vigilancia de la Resistencia a los Antimicrobianos* (VIRA, surveillance of antimicrobial resistance) project, which included 40 hospitals in 15 Spanish autonomous communities, has also confirmed such decrease in penicillin-resistant strains, from 59.8% in 2001 to 30.2% in 2004 (p<0.001) to 14.3% in 2006 (p<0.001)[81,82]. The Carlos III Institute, with strains voluntarily submitted, reported a decrease in penicillin-resistant pneumococcus from 36.1% in the 1997-2001 period to 22.4% in 2007-08, with a statistically significant decrease among resistant strains of 6B, 9V, 19F y 23F serotypes[83]. Regarding macrolides, the decrease could only be observed in children, since for adults it remained stable (22%) through the 1997-2004 and 2004-2008 periods[78].

Unfortunately, this trend has been slightly inverted and, since 2008, a new increase in resistance has been observed. This could be partly explained by the expansion of serotypes not contained in the PCV7, given that some of them have increased their resistance, such as 19A, 15A and 35B[76,84]. This decrease and subsequent increase in antibiotic resistance, due to these serotypes in Spain, has not only been described in IPD-causing strains, but also in strains causing acute otitis media[85]. Such increase has also been documented among Spanish adults, for which serotypes 19A and 3 represented approximately a fourth of all the IPD cases in patients aged 65 or more from 2007 to 2009, while 4 serotypes (19A, 14, 24F and 9V) were responsible for 66.3% of the penicillin non-susceptible strains[86]. In fact, in Spain, an increase of penicillin-resistant strains has been documented among the serotypes not included in the vaccine from 12.0% between 1997-2001 to 49.5% between 2007-08, mainly due to the increase in 19A (3.3% to 24.5%) and 24F (0.1% to 7.6%) serotypes[83]. More specifically, serotype 19A is raising more concerns, since it has increased its MIC to beta-lactam agents 5 times in the 2000-2001 and 2010-2011 periods, and the percentage of penicillin-resistant strains has increased from 18.2% to 71.4% (p=0.003)[87]. Globally, pneumococcus resistance to penicillin is still lower, since it decreased from 54.2% in the 2000-2001 period to 36.9% between 2010 and 2011. In the latest period, it increased in our country, from 22% to 26% between 2008 y 2011[87].

In the USA, an increase of IPD cases by serotype 19A was detected through the 1998-1999 and 2006-2007 periods in subjects younger than 6 (from 2.6% to 47.2%), in adults aged 18 to 64 (from 2.9% to 16.6%) and in those older than 65 (from 3.7% to 14.9%)[88]. Likewise, in 2009 data from a New York study were disclosed. With respect to penicillin, the authors found a decrease from the previous period (1995-1999) to the subsequent period (2002-2006) after introducing the heptavalent conjugate vaccine in MIC_{90}, averages of 1 mg/L to 2 mg/L, an increase of 22% in the proportion of non-susceptible strains (from 27% to 49%, p=0.001) and a risk 2.5 times (1.4-4.4; 95% IC) greater of invasive disease by non-susceptible strains[89]. They also documented an increase in the percentage of erythromycin-resistant strains (from 6.7% to 29.6%; p<0.001), with no changes regarding third generation cephalosporins.

However, PCV13, which includes some of the emergent resistant serotypes, has shown, after its introduction in the United Kingdom, a 70% vaccine efficacy versus the most prevalent serotype in children and adults, the 19A[90]. Such decrease has also been soon described in children in the Madrid Community region, where PCV7 was replaced by PCV13 in June 2010, with a very important reduction of IPD cases by 19A and 1 serotypes, as well as the resistance of *S. pneumoniae*[91].

Among adults with certain underlying pathologies, we might suppose that selective pressure on the pneumococcus could be greater due to a higher consumption of antibiotics and, therefore, the resulting resistance percentages could be higher. A French study on HIV-infected patients showed that resistance to penicillin (56%) in IPD-causing strains in 2000-2011 was superior to that of the general population in the same time period, with no differences in serotypes distribution[92].

23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE

The 23-valent pneumococcal polysaccharide vaccine (PPV23) was included in the Spanish adult immunization scheme in 2003-2005, in the different Spanish regions[93]. The recommended dose pattern is 1 single dose to any person aged 60 years or more and to any person older than 2 years who presents any other risk factor, such as: chronic diseases (cardiovascular, pulmonary (except asthma) or metabolic); functional or anatomic asplenia, chronic kidney disease, hepatic cirrhosis, diabetes mellitus, alcohol abuse, cerebrospinal fluid fistula, cochlear implants, HIV infection, immunosuppressant diseases and chemotherapy treatment[94]. It is currently recommended to re-vaccinate subjects already vaccinated 5 years before (2nd dose) who meet the following circumstances:

- Subjects older than 60 years who had been vaccinated more than 5 years before for any of the previous indications they suffered before reaching the age of 60.

- Subjects of any age with high risk of severe pneumococcal

disease, such as: asplenia, chronic kidney disease, nephrotic syndrome or any other immunosuppression[94].

The results regarding clinical efficacy during the last 30 years have not been conclusive due to the heterogeneity of the methodology and, even meta-analyses are not useful for drawing conclusions, because many of them did not follow research protocols, register numbers or flowcharts[96,97]. Furthermore, most of them did not take into account the quality of assays when assessing them[98]. Regarding PPV23 vaccine effectiveness based on observacional studies, one meta-analysis shows an effectiveness in immunocompetent healthy adults from 50-80% for the prevention of invasive diseases, with no conclusive demonstration of protection against non-bacteremic pneumonia[22]. Regarding the populations pertaining to risk groups, another meta-analysis[99] based on the assessment of 18 randomized and controlled clinical assays, and 7 un-controlled observational case-control or cohort studies, shows that, even though the PPV23 estimated efficacy in healthy adults versus the prevention of IPD was 74% (95% CI 56-85%), in risk patients there was no evidence of protection with this vaccine, or against pneumonia by all causes, or mortality reduction. However, low potency could be the cause. Melegaro et al. included observational studies in their meta-analysis and found a vaccine efficacy against IPD in healthy elderly of 65%, although it did not achieve statistical significance (OR 0.35; 95% CI 0.08-1.49) in this group or among the elderly belonging to risk groups with a vaccine efficacy of 20% (OR 0.80; 95% CI 0.22-2.88)100. They found no benefits against pneumonia. In another meta-analysis, Huss et al. observed a low relative risk (RR) against pneumococcal pneumonia (RR 0.64; 95% CI 0.43-0.96) and pneumonia from any cause (RR 0.73; 95% CI 0.56-0.94) using the data from 8 clinical assays, but they found no benefits in the elderly or adults with chronic pathologies[101].

When specifically assessing the efficacy of PPV23 in patients with COPD, in another recent meta-analysis of the Cochrane[102], no protection was evident against exacerbations [OR 0.58 (95% CI 0.3-1.1)], pneumonia by all causes [OR 0.72 (95% CI 0.5-1.0)] or hospital visits due to upper respiratory infections [OR 1.29 (95% CI 0.68-2.47)] or lower respiratory tract [OR 1.00 (95% CI 0.75-1.33)]. Another clinical assay performed on HIV-infected patients from Uganda with PPV23 versus placebo[103] showed an absence of vaccine efficacy for the prevention of the first IPD episode [-100% (95% CI -100 – 14)] or for the prevention of pneumonia from all causes [–89% (95% CI –100%, –12%)] for this type of African patients. The isolated use of PPV23 in HSCT receptor patients did not show efficacy either because the serologic response rate was below 20% and did not improve after 2 doses[104].

In countries with high vaccine coverage, such as the United Kingdom, where vaccination was extended in 2003 to include all adults aged 65 years or more (75% population vaccinated in 2009-2010), PPV23 vaccine effectiveness observed in the period 2003-2010 was statistically significant for the youngest population, adults aged 65 to 74, and patients with no underlying disease [56% (95% CI 24-75%)][105]. No evidence was observed regarding protection for the population with underlying disease (table 5) or for the population older than 75 years. Regarding serotype-dependent vaccine efficacy, and in the 2 years after vaccination, it was non-significant for 20 of the 23 serotypes. It was only significant for the following serotypes: 7F [74% (95% CI 26-91)], 9N [88% (95% CI 6-98)] and 14 [58% (95% CI 21-77)][105].

In patients with inflammatory bowel disease being treated with anti-TNF or immunosuppressants combined (anti-TNF and thiopurines), PPV23 immunogenicity was decreased[106,107], although the response might be normal in those subjects treated with thiopurines at doses used for those pathologies[108].

Among other inconveniencies already described for this vaccine, the following can be found:

Table 5 **Vaccine efficacy (95% CI) of PPVP23 according to age, presence of underlying diseases and time after vaccination. Adapted from Andrews et al.**[105]

		65-74 years	75-84 years	≥85 years
≤ 2 years after vaccination	Healthy	65 (23-84)	42 (-19 – 72)	-35 (-198- 38)
	Immunocompromised	26 (-55-65)	54 (0-79)	34 (-103-79)
	High-risk immunocompetent	69 (22-88)	70 (36-86)	42 (-57 – 78)
2-5 years after vaccination	Healthy	62 (21-82)	41 (-9-68)	36 (-29-68)
	Immunocompromised	-92 (-252- -5)	48 (8-71)	42 (-20-72)
	High-risk immunocompetent	-13 (-151-49)	-3 (-91-45)	8 (-81-54)
≥ 5 years after vaccination	Healthy	28 (-72 -70)	-9 (-102-42)	16 (-52-54)
	Immunocompromised	17 (-58-56)	17 (-23-57)	32 (-28-64)
	High-risk immunocompetent	7 (-89 – 54)	14 (-45-49)	7 (-66-48)
Any time after vaccination	Healthy	56 (24-75)	27 (-16-54)	14 (-40-47)
	Immunocompromised	-17 (-96-31)	38 (0-62)	35 (-15-64)
	High-risk immunocompetent	21 (-46-57)	23 (-23-52)	11 (-51-48)

- Antibody levels decrease progressively after vaccination until achieving pre-vaccination levels after a period of 3 to 10 years[109].

- Absence of immune memory or anamnestic response[110]. Polysaccharides are antigens recognized by the immune system through surface immunoglobulins in B-lymphocytes, with no intervention of T cells. The stimulated lymphocyte B develops a primary response, characterized by the slow production of antibodies with scarce avidity and affinity for the antigen. Once the B lymphocyte contacts the antigen, there is no memory in the immune system and, after new contact with the same antigen, in the best case, a similar response to the initial one will take place[110].

- Induction to the immune tolerance phenomenon or hyporesponse with revaccinations[111-114]. The immune response to revaccination against most of the serotypes is lower to that observed after the first vaccination, against most of the serotypes. Therefore, the second dose of vaccine is not considered a reinforcement.

- It has no effect on nasopharyngeal colonization, fundamental factor in the epidemiology of pneumococcal infections and, therefore, it does not involve significant protection against pneumococcal infections of mucosa, nor against the decrease in antibiotic-resistant pneumococcal strains[115].

13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV13)

PCV13 is an anti-pneumococcal conjugate vaccine providing protection against 13 serotypes of *S. pneumoniae*[1]. The 13 serotypes of pneumococcus included in this vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) are responsible for, at least, 50-76%[10] of the invasive pneumococcal disease in adults aged 50 or older1. In Spain, data from 2010-2012 indicate that the coverage of PCV13 serotypes is of 63% in immunocompetent adults and of 45% in immunocompromised adults[63] The most frequently identified serotypes were serotype 3 (11.2%), 19A (8.9%) and 7F (8.3%).

PCV13 received European commercialization approval for use in infants and small children in December 2009, and has been available in Spain since July 20101. The impact observed in the use of the vaccine in Spain shows a reduction in the incidence rate for hospitalizations due to invasive pneumococcal disease of 55% ($p<0.001$) in children younger than 15 , which is of 63% ($p<0.001$) in children aged 12 and 24 months[116].

The impact observed is serotype-dependent (as occurred with PCV7), with a decrease observed in the Community of Madrid (Heracles study) of 67% ($p<0.001$) in the incidence rate for IPD for the 13 vaccine serotypes, mainly at the expense of the reduction in the serotype 19A incidence (87%, $p<0.001$) and serotype 1 incidence (47%, $p<0.01$)[91,117,118]. Regarding the impact on the reduction depending of clinical form, 2 years after its inclusion, a decrease ($p<0.05$) in hospitalizations due to bacteremic pneumonia (74%), pneumonia complicated with pleural effusion (45%) and meningitis (54%) has been observed[118]. These data correlate with those observed in other countries, such as the USA[119] and the United Kingdom[90].

Recently, the European Medicines Agency (EMA) approved their use as an active immunization for the prevention of invasive diseases caused by *S. pneumoniae* in adults aged 50 or older[1]. The approval of this new indication is based on clinical data of immunogenicity and safety obtained from more than 6,000 adults, aged 50 to 95 years, including adults aged older than 65 previously vaccinated with one or more doses of anti-pneumococcal polysaccharide vaccine of 23 serotypes (PPV23)[1]. Serotype-specific OPA (opsonophagocytic activity) functional antibodies titers as subrogation measure to assess the potential efficacy of PCV13 against invasive pneumococcal disease and pneumonia. Every study included healthy adults and immunocompetent patients with underlying diseases (such as pulmonary, liver, kidney or cardiovascular chronic diseases, and alcoholic liver disease and diabetes mellitus) and with certain habits, like smoking or alcohol abuse, which have been described as risk factors for pneumococcal infection1. In the USA, the technical datasheet approved by the FDA includes, apart from the invasive pneumococcal disease, the indication for pneumonia prevention in adults aged 50 years or more[120].

The pivotal study performed with adults who had not previously received PPV23, included subjects aged 60 to 64 who were randomly assigned to receive one dose of PCV13 or PPV23, and aged 50 to 59 who received a single dose of PCV13. One month after vaccination, adults aged 60 to 64 demonstrated a non-inferiority of the functional immune response for the 13 serotypes and superiority for 9[121]. When comparing immune responses obtained after one single dose of PCV13 in both age groups, the adults aged 50-59 presented responses being superior for 9 out of the 13 serotypes, compared to those obtained for the 60-64 years group. This highlights the importance of age in immune response[121,122]. An extension of the initial study was performed aimed at assessing the response to a second PCV13 or PPV23 dose administered 3.5 and 4 years later. The results obtained one month after the second PCV13 or PPV23 dose showed the superiority of the functional immune response for most of the common serotypes in the cohorts who had initially received PCV13 in the previous study[122,123]. These results demonstrate that PCV13 makes the immune system more susceptible to generating a booster response with the second administration of any of the two vaccines and, therefore, that the conjugate vaccine induces immunological memory. On the contrary, when PPV23 was administered as a second dose to those subjects who had initially received this same vaccine, lower responses were obtained for 8 out of the 12 serotypes in comparison with those obtained after the first PPV23 dose[122,123]. Figure 1 shows the immune response against serotype 1, which illustrates the sequence with most of the serotypes. This result confirms the hyporesponse associated to polysaccharide vaccines[122]. In a pivotal study performed on adults aged 70 years or more, who had been vaccinated with PPV23 at least 5 years before being included in the study, compared the OPA functional antibodies titers obtained one month after having received a single dose of PCV13 or PPV23. The results indicated that immunological responses obtained after the administration of PCV13 were non-inferior for 12 serotypes and superior for 10 of the common serotypes and for 6A, in a statis-

tically significant manner, when compared to responses obtained with PPV23[124].

In HIV-infected patients, who are at a greater risk for IPD, the serological response against PPV23 and PCV13 has been compared, although in a study including 202 patients, there were no differences after 4 weeks[125].

In another study with 104 patients not previously vaccinated, and paired according to CD4 levels, after 48 weeks a better and statistically significant response was observed in those subjects who received PCV13 versus, at least, 2 serotypes (37.5% versus 20.2%, p=0.006)[126].

In these patients, a very significant decrease of antibody levels has been shown 5 years after the vaccination with PPV23, even with a good virologic and immunological control[127]. There are immunogenicity and safety data for PCV13 in subjects aged 18 years or more and infected with HIV who had been previously vaccinated with at least 1 dose of PPV23 (160 subjects had received 1 previous dose of PPV23 and 169 at least 2 doses of PPV23) administered at least 6 months before[128]. The vaccine schedule was of 3 doses of PCV13 at 0, 6 and 12 months. All the subjects had a CD4 level ≥ 200 cells/mm^3 and a viral load <50,000 copies/mL. The results show that PCV13 immunogenicity (measured as GMC of IgG and specific serotype OPA) was similar after each of the administered PCV13 doses, with no differences based on having previously received 1 or 2 doses of PPV23 (figure 2). Even for some serotypes (6A, 6B, 9V, 18C, 19F and 23F) the response was superior with the subsequent doses, although the clinical significance of this finding is yet unknown. The safety profile observed for all the patients was acceptable[128]. By serotype coverage, one French study estimated that PCV13 covered 70% of the cases in these patients, versus 78% of the PPV23[92].

In HSCT receptor and donor patients, when replacing PCV7 with PCV13, international consensus recommendations were updated in order to include the PCV13[129]. There are no current assays with PCV13 published. However, their use is recommended as PCV7 substitution where it is not available. Recently, the recruitment period of a phase III study with allogeneic HSCT, assessing the efficacy and safety of PCV13 (ClinicalTrials.gov Identifier NCT00980655), with a design almost identical to that published by the European group of transplants[130]. Unlike what happens with PPV23, donor vaccination with a conjugate pneumococcal vaccine does increase significantly the responses in the receptor[131]. In clinical practice, donor vaccination is not used, but could be an opportunity to update its schedule and also benefit the receptor's transplant.

Among patients in IPD risk groups who have suffered a previous episode of pneumococcal pneumonia, Musher et al. confirmed that the subsequent response to the vaccination, once treated, lasted longer with PCV7 than with PPV23. That is because, despite being similar at weeks 4-8, after 6 months, the antibody levels after the polysaccharide vaccine descended to baseline levels[132].

PCV13 safety was assessed in more than 6,000 adults, 1,916 of which had previously received the PPV23 vaccine. The adverse reactions very frequently reported in clinical assays were: local reactions at the administration site (erythema, swelling, pain, arm movement limitation) and systemic events like decreased appetite, headache, diarrhea, rash, shivering, fatigue, arthralgia and myalgia.

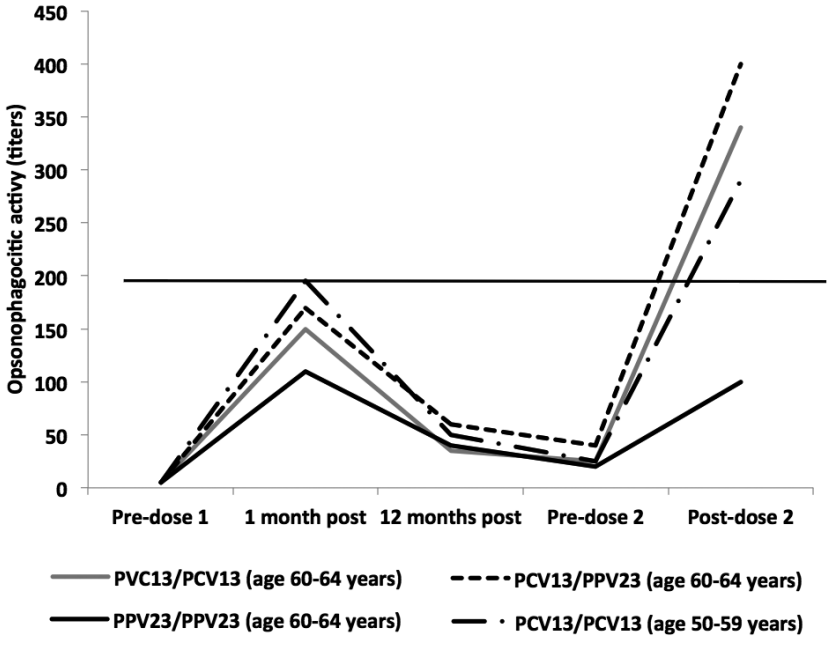

Figure 1 Immune response against serotype 1 after the different vaccine patterns in the pivotal study of non-inferiority (assay 004)[122]

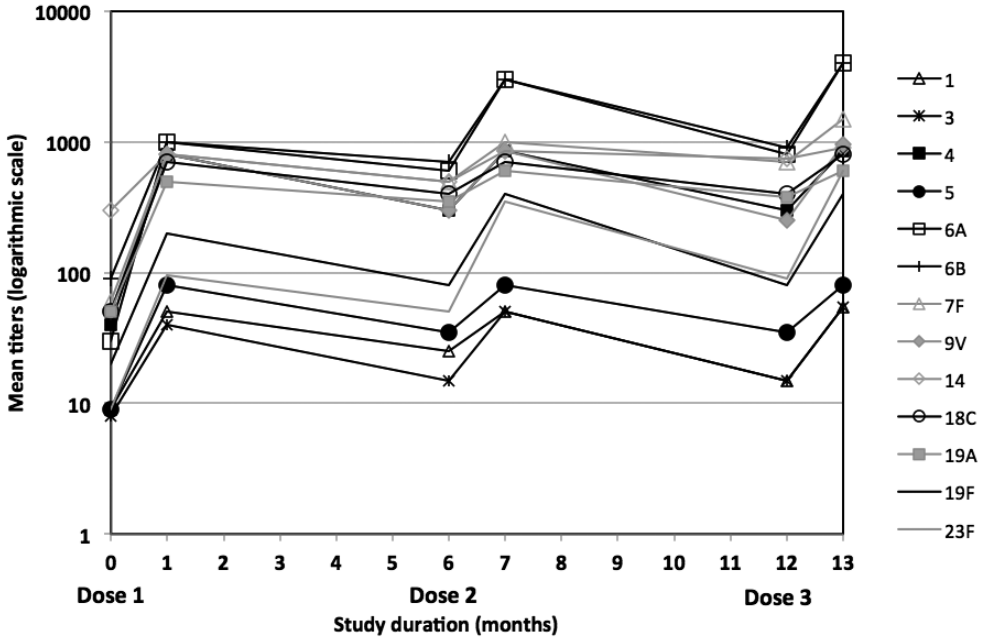

Figure 2 | **Immune response to PCV13 in HIV-infected patients having previously received vaccine with 1 or more doses of PPV23**[128]

Subjects older than 65 years reported fewer adverse reactions than younger individuals, regardless of the previous vaccination status with PPV23.

No significant differences were observed regarding the frequency of adverse reactions when PCV13 was administered to subjects previously vaccinated with PPV23[1]. In HIV-infected patients, it has been assessed the impact that PCV7 could show, specifically on clinical, virological and immunological evolution in these patients. It has been shown to be safe, with no effect on CD4 counts or on the viral load in patients receiving antiretroviral treatment[133]. According to the results of two studies performed with subjects aged 50 to 59 years and 65 years or more, PCV13 can be administered concomitantly with the inactivated trivalent vaccine against influenza virus[1].

AVAILABLE DATA FOR POPULATIONS AT RISK WITH ANTI-PNEUMOCOCCAL CONJUGATE VACCINES PCV7 AND/OR PCV9

There are 2 clinical assays for the efficacy of conjugate vaccines published for patients infected with HIV (table 6).

With the exception of the data previously presented regarding clinical efficacy in patients infected with HIV, the data provided below are related to immunogenicity and safety studies in patients at high risk for IPD (table 7).

COST-EFFECTIVENESS OF ANTI-PNEUMOCOCCAL VACCINE IN ADULTS

It is not easy to draw conclusions on the cost-effectiveness value of anti-pneumococcal vaccination in adults with underlying pathologies[163]. Although various studies have been performed on infant populations with very favorable results supporting the use of an anti-pneumococcal conjugate vaccine, data regarding adults with the polysaccharide vaccine are scarce but favorable[164]. Before the introduction of PCV7 in children, a study in 10 European countries, including Spain, assessed the cost-effectiveness of PPV23 to prevent IPD in adults, and it was found to be acceptable in all countries[165]. With respect to Spain, the cost-effectiveness index per QALY among adults aged 65 years or older, was estimated to be 9,187 euros.

Since the appearance of conjugate vaccines, the evidence is more variable because an important effect of indirect protection has been observed regarding adult population in those countries where PCV7 had been introduced into the infantile vaccination schedule[88]. It has been proven that, despite the decrease of IPD cases due to vaccine serotypes in adults in the USA, the proportion of IPD cases in adults with anti-pneumococcal vaccine indication has increased from 51% before the introduction of PCV7 to 61% after it (p=0.0001)[166]. Another study in the United Kingdom shows that the use of PPV23 can still be considered a cost-effective measure for older adults and high risk patients, after the introduction of PCV7[105].

Table 6 **Clinical assays with pneumococcal conjugate vaccines in HIV+ populations.**

Author	Study population. Design	Vaccination pattern		Results
		Treatment group	Control group	
French, NEJM2010[134]	Adults (n=496) infected with HIV in Malawi with 1 previous IPD episode; 2003-2007	2 doses of PCV7* (n=248)	Placebo (n=248)	Vaccine efficacy against IPD by serotypes included in the PCV7 vaccine and 6A: 74% (30%, 90%) Vaccine efficacy against pneumonia by all causes: 25% (-19%, 53%)
Klugman, NEJM 2003[135]	Children (n=39,836) infected with HIV in South Africa; 1998-2000	3 doses of PCV9** (n=19,922)	Placebo (n=19,914)	Vaccine efficacy against IPD by serotypes included in PCV9 vaccine: 65% (24%, 86%); p=0.006 Vaccine efficacy against pneumonia by all causes: 13% (-7%, 29%); p=0.19

*VNC7: 4, 6B, 9V, 14, 18C, 19F y 23F
**VNC9: 1, 4, 5, 6B, 9V, 14, 18C, 19F y 23F

In Germany, another model also estimates it as a cost-effective strategy, despite the changes originated by infantile systematic vaccination (incremental cost of 17,065 euros per QALY gained)[167].

This phenomenon of indirect protection observed for PCV7 is likely to take place again after its replacement by PCV13 in infantile schedules, which will partly decrease the cost-effective value of its systematic use in adults in general, both of PCV13 and PPV23[168]. However, the indirect cost requires several years to become evident and will only be visible in those countries systematically administering vaccines to all their children.

In a model in Italy (a country were children systematically receive PCV13 vaccine), systematic vaccination with such vaccine in adults aged 65 years or older proved to be cost-effective with costs per QALY from 17,000 to 22,000 euros, depending on the strategy used, which could vary based on the number of cohorts to be vaccinated[169]. In Germany, assuming a comparable effectiveness between PCV7 and PCV13, another model has shown that vaccination strategy with PCV13 in adults aged older than 50 years and adults belonging to high risk groups, is more cost-effective than the vaccination with PPV23, and also than no vaccination[170]. According to that model, every euro invested in PCV13 saves €2.09 (€2.16 from a societal point of view) compared to PPV23.

If we bear in mind that more than 80% of IPD cases correspond to bacteremic pneumonia, but that they only represent approximately 20% of the cases of pneumococcal pneumonia, we get an idea of the huge cost-effective impact that any level of protection would have against non-bacteremic pneumococcal pneumonia[171].

In fact, a cost-effectiveness analysis for PCV13 for high risk adults performed in England (where children are systematically vaccinated with this vaccine), Rozenbaum et al. conclude that it is unlikely that its use will become cost-effective for this population due to the indirect effect of infantile vaccination. The only groups for which it was cost-effective were patients with chronic liver disease and HIV-infected patients. However, it also pointed out that the effectiveness that PCV13 could show against non-bacteremic pneumococcal pneumonia would substantially reduce such association, especially among high risk group adults[168]. The same authors, in a model based on the Dutch population published 2 years before, they concluded that both in the adult population aged 65 years or more, and in high risk group adults, vaccination with PCV13 was a cost-effective measure[172]. In the USA, vaccination with PCV13 for adults aged 65 years or older, as well as high risk groups of patients, was estimated to be more cost-effective than vaccination with PPV23 (28,900 dollars per QALY and 11,300 when considering only adults aged 65 receiving 1 dose), although assuming a certain degree of protection against non-bacteremic pneumonia for which PCV13 is indicated for adults in that country[173,174]. Another American model that considered adults aged 50 years or more, also found a greater impact on the total burden of pneumococcal disease with PCV13 than with PPV23 (3,500 million dollars reduction of health-care costs and 7,400 million of social costs)[175]. The estimated annual cost of hospitalizations due to CAP, for the 2003-2007 period in Spain was 480 million euros (€5,353 per case)[13]. In a study performed in Badalona (Barcelona, Spain), the cost of CAP due to pneumococcus per hospitalized patient was estimated to be €2,465 and €568.48 per ambulatory patient[23].

VACCINATION RECOMMENDATIONS FOR ADULTS WITH UNDERLYING PATHOLOGIES

Despite current therapeutic and preventive measures, the incidence and mortality of pneumococcal disease in adults

Table 7 **Immunogenicity and safety studies with conjugate vaccines in high risk populations for IPD**

Clinical group	Population	Conclusions
Infected with HIV[136-143]	Adults and children infected with HIV	PCV(7/9) has demonstrated effectiveness for the prevention of invasive pneumococcal disease in patients infected with HIV vs. PPV23. PCV7 is immunogenic and safe in adults infected with HIV regardless of previous vaccination status with PPV23. Superiority of the response to PCV vs. PPV23.
Hematopoietic stem cell transplantation[130, 144-149]	Studies in allogeneic and autologous hematopoietic stem cell transplantation in adults and children (receptors and donors)	Early vaccination start is recommended after transplantation (3 months) with 3 doses of PCV7, as well as one dose of PPV23 at least 12 months after the PCV7. PCV7 induces antibodies in the appropriate titers and functioning after the opsonophagocytic assay. Seroprotection rates around 80%. In multivariable analyses by logistic regression, the only factor significantly affecting vaccine response was the type of vaccine, with an OR of 8.85 favoring PCV7, compared to PPV23. The booster effect of PCV7 over PPV23 has been demonstrated. PCV7 is safe in autologous hematopoietic stem cell transplantation donors and receptors. Patient' responses improve when the donor has been vaccinated.
Cancer[150]	Patients with chronic lymphocytic leukemia (CLL)	Patients with CLL present significantly lower responses to PCV when compared to a healthy subjects. Early vaccination (before chemotherapy) improves the response to the vaccine.
In immunosuppressant treatment[106-108, 151-154]	Patients with rheumatoid arthritis or spondyloarthropathy and juvenile idiopathic arthritis being treated with methothrexate or with anti-TNF drugs	PCV7 is safe and immunogenic in most children with JIA in immunosuppressant treatment, including anti-TNF agents (Etanercept). Anti-TNF inhibitors have no significant effect on post-PCV7 antibody response (1 dose). Receiving treatment with MTX and an advanced age are factors predicting an insufficient response to PCV7 in patients with chronic arthritis.
	Patients with inflammatory bowel disease being treated with thiopurines or anti-TNF drugs	PPV23 has proved to be safe and effective in patients treated with thiopurines. The doses used of these drugs do not show an immunosuppressant effect on cell and immune responses. Anti-TNF drugs, alone or in combination with other immunosuppressant drugs, reduce the response to PPV23.
Chronic kidney disease[155, 156]	Paediatric patients with chronic kidney disease, including the idiopathic nephritic syndrome (INS)	Haemodialysis does not interfere with the response to vaccination with 2 doses of PCV7. Children with INS may present an immune response to PCV7, with persistence of antibody levels for at least 1 year.
Asplenia[157,158-161]	Adult and pediatric patients	1 single dose of PCV7 is sufficient for vaccination in asplenic subjects, even for those previously vaccinated with PPV23. An important immune response has been observed against PCV7, which is maintained even 5 years after the vaccination.
Chronic respiratory disease[14, 162]	COPD patients	PCV7 induces a superior immune response vs. PPV23 in patients with COPD 2 being persistent for 2 years after vaccination. Being previously vaccinated with PPV23 reduced the response of a posterior dose of the PCV7 vaccine.

Table 8 Vaccination recommendations for adults with underlying pathologies

	NO PREVIOUS VACCINATION	PREVIOUS VACCINATION WITH PPV23 (≥ 1 YEAR)
IMMUNOSUPPRESSED[2,3] (table 9) CSF FISTULA COCHLEAR IMPLANTS ANATOMIC OR FUNCTIONAL ASPLENIA	PCV13 ---> PPV23 (minimum interval 8 weeks)	PCV13 A second PPV23 dose after 5 years or more from the previous
IMMUNOCOMPETENT WITH OTHER UNDERLYING DISEASES (table 9)	PCV13	PCV13

[1]Re-vaccination with a 2nd dose of PPV23 with a minimum interval of 8 weeks after PCV13 if the administration of the 1st dose of PPV23 was more than 5 years before, up to a maximum of 2 doses.
[2]Patients who undergo a hematopoietic stem cell transplant, according to International consensus recommendations[176], shall receive 3 doses of PCV13 vaccine (starting 3 months after the transplant) with a minimum interval of 1 month between doses and 1 dose of PPV23 starting 8 weeks after the last PCV13 dose provided the transplant has taken place 12 months before. If there is a chronic GVHD, such dose reinforcement dose of polysaccharide vaccine is recommended to be replaced by a dose of conjugated vaccine.
[3]Patients in treatment with methothrexate or rituximab could require 2 doses of PCV13 vaccine or wait 1-3 months after finishing treatment.

Table 9 Patients considered as immunosuppressed or immunocompetent with other underlying pathologies or risk factors.

SUBJECTS CONSIDERED AS IMMUNOSUPPRESSED OR IMMUNOCOMPROMISED	- Hodgkins disease, leukemia, lymphoma - Multiple myeloma - Stage 4-5 chronic kidney disease[1] - Stage 3[2] chronic kidney disease with an increased risk (nephritic syndrome, diabetes mellitus or immunosuppressant treatment) - Solid organ or hematopoietic stem cell transplantation[3] - Chemotherapy or immunosuppressant treatment[4] - HIV infection[5] - Autoimmune inflammatory rheumatoid disease[6] - Inflammatory bowel disease (includes Crohn's disease and ulcerous colitis)[7]
IMMUNOCOMPETENT SUBJECTS WITH OTHER UNDERLYING PATHOLOGIES OR RISK FACTORS	- Chronic respiratory disease (includes COPD, severe asthma[8], and diffuse interstitial lung disease) - Chronic liver disease (includes cirrhosis) - Chronic cardiovascular disease (includes coronary heart disease, congestive heart disease and cerebrovascular accident) - Diabetes mellitus treated with OAD or insulin-dependent subjects - Smoking[9] - Alcohol abuse[10]

[1]Situation in which the patient maintains an estimated glomerular filtration inferior to 30 ml/min/1.73 m^2. The measurement of eGFR is based on the measurement of standardized serum creatinine and the application of the CKD-EPI formula[55].
[2]Situation in which the patient maintains an estimated glomerular filtration between 30-59 ml/min/1.73 m^2.
[3]If the patient was waiting for a solid organ transplant, vaccination should take place 2-4 weeks before. If the transplant has already taken place, wait 6 months. In hematopoietic stem cell transplantation, vaccine is not recommended before the transplantation, but is recommended after 3-6 months.
[4]Vaccination at least 10-14 days before starting treatment (preferably 4-6 weeks) or 3 months after completing chemotherapy or radiotherapy treatment. Subjects vaccinated during treatment (or in the 2 weeks previous to starting treatment, will require a new vaccination 3 months after finishing such treatment.
[5]Preferible with the best immune state (generally above 200 cells CD4/mm^3)
[6]Vaccine shall be administered during the steady state of the disease. It can be administered during the treatment with anti-TNF, but it is preferably before starting methothrexate or rituximab, or 1-3 months after finishing it.
[7]It is advisable to administer the vaccine when diagnosis of the disease takes place. Vaccination is safe during the treatment with immunosuppressants and biologic drugs. Thiopurines have not demonstrated being able to decrease vaccine efficacy. Anti-TNF drugs, methothrexate or the combination of drugs decrease its efficacy. Therefore, it is preferable to administer the vaccine before starting those drugs.
[8]High risk asthma patients (one or more hospitalizations or visits to ER; use of oral corticoids).
[9]Includes active smokers with a load of 15 or more years/package with no comorbidity, ex-smokers with a load of at least 20 years/package and who have been less than 10 months without smoking; and any other smoker regardless of his/her age, and intensity and/or load, who suffers a respiratory disease.
[10]Includes subjects with alcohol abuse problems and alcohol dependence syndrome. Those subjects who consume more alcohol than the healthy risk limits: in men, more than 28 standard drinks/week and in women, more than 17 standard drinks/week. (standard drinks: Standard units for drinks that correspond to 10 grams of pure alcohol present, for example, in a glass of wine (100 cm^3), a beer (200 cm^3) or half glass of whisky (25 cm^3))[177].

with underlying diseases remains high, which justifies the need for strengthening and increasing awareness, and for prevention strategies for this high risk population and the health care professionals who treat them.

According to what has been previously described, adults with underlying pathologies included in tables 8 and 9 should receive the vaccine against pneumococcus and, preferably, receive at least 1 dose of PCV13, which will always be administered first.

On July 17th, 2012, the Spanish *Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia* (General Directorate for the Basic Portfolio of Services of the National Health and Pharmacy System) resolved to include the pharmaceutical provision of the Health System financed with public funds, of the indication for the active immunization for the prevention of invasive diseases caused by *S. pneumoniae* in adults aged 50 or more, with the following indications: Immunosuppression: Hodgkin's disease, leukemia, lymphoma, multiple myeloma, renal insufficiency, nephrotic syndrome, solid organ or hematopoietic stem cell transplantation, chemotherapy treatment or HIV infection. After the recent positive opinion of the CHMP of the EMA for the extension of the indication to adults aged older than 18 years, the Spanish National Health and Pharmacy System will probably modify such provision as well soon. In turn, certain Spanish Autonomous Communities have extended the aforementioned indications and the age ranges. For some of the recommendations made in this consensus document (tables 8 and 9), there is no public funding now. Therefore, they will have to be prescribed with consumers bearing the full cost.

Table 8 describes vaccine patterns taking into account serotype coverage of PCV13 vaccine at 63% in immunocompetent adults and 45% in immunocompromised patients[63].

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