



Transworld Research Network  
37/661 (2), Fort P.O.  
Trivandrum-695 023  
Kerala, India

Recent Advances in Pharmaceutical Sciences II, 2012: 69-87 ISBN: 978-81-7895-569-8  
Editors: Diego Muñoz-Torrero, Diego Haro and Joan Vallès

## 5. Is the 23-valent pneumococcal polysaccharide vaccine useful in preventing community-acquired pneumonia?

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**Abstract.** Although bacteremic pneumococcal pneumonia is the most severe form of pneumonia, non-bacteremic forms are much more frequent. Laboratory methods for the diagnosis of non-bacteremic pneumococcal pneumonia have a low sensitivity and specificity, and therefore all-cause pneumonia has been proposed as a suitable outcome to evaluate vaccination effectiveness.

This work reviews the epidemiology of community-acquired pneumonia (CAP) and evaluates the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV-23) in preventing CAP requiring hospitalization in people aged  $\geq 65$  years.

We performed a case-control study in patients aged  $\geq 65$  years admitted through the emergency department who presented with clinical signs and symptoms compatible with pneumonia. We included 489 cases and 1,467 controls and it was obtained a vaccine effectiveness of 23.6 (0.9-41.0). Our results suggest that PPV-23 vaccination is effective and reduces hospital admissions due to pneumonia in the elderly, strengthening the rationale for vaccination programmes in this age group.

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## Introduction

Pneumonia is an inflammation of the lung parenchyma located below the terminal bronchioles (respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli) that leads to impaired gas exchange. The inflammatory reaction causes water density in chest X-rays, the hallmark of pulmonary consolidation. Pneumonia acquired outside the hospital is known as community-acquired pneumonia (CAP), in contrast to nosocomial pneumonia, which is acquired after 48 hours of admission to the hospital or the first week after discharge [1].

Pneumonia together with influenza is the seventh leading cause of death in the United States of America (USA) with a high estimated monthly mortality rate of 19.4/100,000 inhabitants [2].

On the basis of a study it was estimated roughly 915,900 cases of CAP could occur annually among seniors in the USA and that approximately 1 of every 20 persons aged  $\geq 85$  years could have a new episode of CAP each year [3]. Other studies estimated a number of cases of CAP requiring hospitalization in USA of 485,000 patients annually, and 43,000 of these persons died [4].

Currently, an etiologic diagnosis is achieved in between 29 and 60% of cases of CAP requiring hospital admission, depending on the number of samples and techniques used [5-16]. In some studies, the rate exceeds 70% [17-19], although the percentage of etiologic diagnoses may be significantly lower in hospitals without systematic diagnostic protocols or when patients have received prior antibiotic treatment, with some studies finding rates of 14% [20] (Tables 1 and 2).

CAP is caused by a wide variety of bacterial species, including, in order of frequency, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophila* and some enterobacteria [22]. Viral infections result in 10-25% of CAP, but the relative frequency of the different microorganisms varies according to factors such as age, underlying disease and the diagnostic methods used [23].

Various studies suggest that between 30 and 50% of cases of CAP requiring hospitalization are caused by *S. pneumoniae* [6, 8, 24, 25].

Some authors have suggested that the number of cases caused by *S. pneumoniae* is underestimated. A Spanish study found that many patients hospitalized with CAP in whom no etiologic diagnosis is obtained using routine techniques are diagnosed with pneumococcal pneumonia when more-sensitive detection techniques are used and samples are obtained by non-routine procedures such as transthoracic puncture [18, 26]. Ruiz-González *et al.*

**Table 1.** Percentage of etiologic diagnostic in several studies about CAP in Spain.

Author, year	Place, period	Hospitalized patient (%)	N	Etiologic diagnostic (%)	<i>Streptococcus pneumoniae</i> (%)
Blanquer, 1991 [13]	Valencia, 1985-1986	91	510	55.1	14.5
Gómez, 1996 [11]	Murcia, 1991-1994	-----	342	29	12.6
Santos de U, 1998 [21]	Mallorca, 1992-1994	26	91	52.7	9.8
Ruiz-González, 1999 [18]	Lleida, 1993-1994	71	109	50 83*	17 30*
Ruiz, 1999 [7]	Barcelona, 1996-1997	100	395	46	16.5
Sopena, 1999 [6]	Badalona, 1994-1996	88	392	58	23.9
Rosón, 2001 [8]	Hospitalet de Llobregat, 1995-1997	100	533	53.1	25.3

N=number of CAP studied.

\*Percentage obtained after tests on samples of lung tissue.

found that 33% of cases of pneumonia labelled as of unknown etiology using standard methods (blood culture, sputum culture and serology) were finally diagnosed as pneumococcal pneumonia after tests on samples of lung tissue obtained by transthoracic puncture [18].

Studies show that the incidence of CAP varies according to several factors: the country where the study is carried out, the age groups included, whether the study includes all patients with CAP or only those requiring hospitalization, and sex [27, 28].

In Spain, the incidence of CAP in adults ranges between 2 and 10 cases per 1,000 persons/year, and from 2.3 to 35 per 1,000 persons/year in people aged  $\geq 70$  years [21, 27, 29, 30]. The incidence of CAP is always greater in the elderly and persons with underlying diseases, which, together with the ensuing mortality, is a concern for health authorities [25]. Tables 3 and 4 show figures of incidence in diferents studies in Spain and other countries.

**Table 2.** Percentage of etiologic diagnostic in several studies about CAP in other countries.

Author, year	Place, period	Hospitalized patient (%)	N	Etiologic diagnostic (%)	<i>Streptococcus pneumoniae</i> (%)
Bohte, 1995 [16]	Leiden (Holand), 1991-1993	100	334	62	27
Porath, 1997 [17]	Israel, 1991-1992	100	346	80.6	42.8
Jokinen, 2001 [24]	Kuopio (Finland), 1991-1982	44	345	53.4	41
Bochud, 2001 [15]	Switzerland, 4 years	8.2	170	54.1	20
Lim, 2001 [19]	Nottingham (U K), 1998-1999	100	267	75	48

N=number of CAP studied.

**Table 3.** Incidence of CAP in Spain.

Author, year	Place, period	Population	Age	N cases	Global Incidence*	Incidence in specific groups**
Almirall, 1993 [31]	Maresme, 1990-1991	39,793	≥14	105	2.6	----
Aguirre, 1993 [32]	Andoain, 1991-1992	8,862	≥14	97	8.8	----
Santos de U, 1998 [21]	Mallorca, 1992-1994	60,450	>14	91	1.8	≥65: 2.3
Almirall, 2000 [27]	Maresme, 1993-1995	74,368	≥14	241	1.6	≥65: 3.2 M: 5 W: 2
Gutiérrez, 2006 [28]	Vinalopó (Alicante), 1999-2001	200,430	>14	493	1.2	65-74: 2.4 ≥75: 5.3 M: 8.7 W: 3.0
Ochoa, 2008 [29]	Tarragona, 2002-2005	11,240	≥65	946	14	65-74: 9.9 ≥85: 29.4

\*cases/1000 persons/year. \*\*cases/1000 persons/year in specific groups: age (years) and gender. M: men; W: women

**Table 4.** Incidence of CAP in other countries.

Author, year	Place, period	Population	Age	N cases	Global Incidence*	Incidence in specific groups**
Woodhead, 1987 [33]	Nottingham (United Kingdom), 1984-1985	53,137	15-79	251	4.7	----
Jokinen, 1993 [34]	Koupio (Finland), 1981-1982	46,974	>1month	546	11.6 M:13.9 W:9.4	<5: 36.0 5-14:16.2 15-19: 6.0 60-74: 15.4 ≥75: 34.2
Myles, 2009 [35]	United Kingdom, 1991-2003	----	All	56,332	2.3	<5: 1.9 ≥65: 6.7
Marston, 1997 [4]	Ohio (USA), 1991	1,014,000	≥18	2,776	2.7	18-44:0.9 45-65:2.8 ≥65:10.1

\*cases/1000 persons/year. \*\*cases/1000 persons/year in specific groups: age (years) and gender. M: men; W: women

Although the criteria for hospitalization are not homogeneous, it is estimated that between 12 and 50% of patients with pneumonia require hospital admission [30-32, 36]. The figures increase with age and can reach between 67% and 75% in cases of CAP in people aged  $\geq 65$  years [29, 34], although some studies have reported figures of 73.2% for all ages [28].

The case-fatality rate of CAP is related to the severity of the disease and is lower in series that include patients treated as outpatients [27, 28, 31, 33, 34, 37] in which the rate is  $\leq 5\%$ , with some studies finding no fatalities [21, 32] (Table 5).

The case-fatality rate is higher in patients requiring hospitalization. In Spain, several series have reported a rate of around 7% in patients of all ages hospitalized for pneumonia [28, 38] with age-related increases being observed.

The case-fatality rate is much higher in cases of CAP requiring intensive care unit admission [37, 39], with a mean of 36.5% [37] and a range of 20-53% according to the study [40].

Taken together, these data show that the incidence and case-fatality rate of CAP are high and, therefore, strategies aimed at their reduction should be sought.

The 23-valent pneumococcal polysaccharide vaccine (PPV-23) has been available in the USA for 25 years and is currently available in most developed countries.

**Table 5.** Hospitalization and case-fatality rate in CAP.

<b>Author, Year</b>	<b>Place, periode</b>	<b>Age</b>	<b>N</b>	<b>Hospitalization (%)</b>	<b>Case-fatality rate (%)</b>
Woodhead, 1987 [33]	Nottingham (United Kingdom), 1984-1985	15-79	251	22	3 0.5 (outpatients) 11 (hospitalized)
Almirall, 1993 [31]	Maresme, 1990-1991	≥14	105	50.4	1
Aguirre, 1993 [32]	Andoaín, 1991-1992	≥14	97	12.4	0
Jokinen, 1993 [34]	Koupio (Finland), 1981-1982	>1month	546	42	4
Fine, 1996 [37]	Meta-analysis	>18	33,148	-----	5.1 13.6 (hospitalized) 36.5 (ICU admitted)
Santos de U, 1998 [21]	Mallorca, 1992-1994	>14	91	26	0
Almirall, 2000 [27]	Maresme, 1993-1995	>14	241	61.4	5 8 (hospitalized)
Gutiérrez, 2006 [28]	Vinalopó (Alicante), 1999-2001	>14	493	73.2	4.8 0 (outpatients) 6.6 (hospitalized)
Ochoa, 2008 [29]	Tarragona, 2002-2003	>65	946	75	13.6 2 (outpatients) 15 (hospitalized)

N=number of CAP studied.

The effectiveness of the 13-valent polysaccharide vaccine, the forerunner of the current PPV-23 was demonstrated in randomized controlled trials in young adults in the 1970s [41-43].

Since 1984, vaccination has been recommended for persons aged ≥65 years and people aged ≥2 years with risk factors [25, 44, 45].

The current consensus is that observational studies have shown that the PPV-23 is effective in preventing invasive pneumococcal disease [42, 46, 47]. However, vaccination coverages are not high in some countries due to doubts about the effectiveness of the PPV-23 in preventing non-bacteremic pneumococcal pneumonia [42, 46, 47].

Although bacteremic pneumococcal pneumonia is the most severe form, non-bacteremic forms are much more frequent [25], with only 10-20% of cases of pneumococcal pneumonia in adults being bacteremic. Since laboratory

methods for the diagnosis of bacteremic pneumococcal pneumonia have a low sensitivity and specificity, all-cause pneumonia has been proposed as a suitable outcome to evaluate the effectiveness of vaccination [42]. If a significant proportion of cases of CAP admitted to hospital are of pneumococcal origin, and vaccination is effective against bacteremic and non-bacteremic forms, this should result in a reduction in hospitalizations for all-cause CAP.

In 1999, various Spanish regions introduced PPV-23 vaccination for patients aged  $\geq 65$  years into the vaccination schedule [45], in accordance with international recommendations [44].

Vaccine coverage in some regions reached 35% in 2001, and 40% thereafter [48]. This coverage and the large number of hospitalizations for CAP in Spain made it possible to establish the objective of this study: To evaluate the effectiveness of PPV-23 in preventing cases of CAP requiring hospitalization in people aged  $\geq 65$  years.

## 1. Methods

### Study design

A matched case-control study in patients with CAP admitted to five hospitals in three Spanish regions between 1 May 2005 to 31 January 2007 was carried out [49].

A case was defined as a person aged  $\geq 65$  years admitted to hospital through the emergency department who presented with an infiltrate on chest X-ray compatible with pneumonia and one or more of the following symptoms or signs of acute lower respiratory tract infection: cough, pleuritic chest pain, fever  $>38^{\circ}\text{C}$ , hypothermia  $<35^{\circ}\text{C}$  or dyspnea within the past 24 hours [25, 50]. Exclusion criteria were institutionalized patients, patients with nosocomial pneumonia (onset  $\geq 2$  days after hospital admission), patients whose initial diagnosis of pneumonia was not confirmed during the hospital stay and cases of CAP in whom the pneumococcal and influenza vaccination status could not be determined

Three hospital controls were selected for each case. Controls were admitted through the emergency department with a diagnosis other than pneumonia, selected from the admission lists of each participating hospital. On selection, the vaccination status of controls was not known and, if the status could not be determined later, they were excluded.

For each case and control information on age, sex, dates of hospitalization and discharge (alive or dead), history of pneumonia, visit to the doctor in the past year, smoking, risk-consumption of alcohol and the presence or absence of underlying conditions was obtained. The pneumococcal and influenza vaccination status was also collected.

Each case was classified according to the level of risk and the degree of immunosuppression associated with the underlying disease: Stratum I (high risk) included all patients with conditions associated with immunocompromise, stratum II (moderate risk) included immunocompetent patients with one or more high-risk medical conditions and stratum III included patients not included in strata I or II (Table 6).

Each case was matched with three control subjects by sex, age (+/- 5 years), date of hospitalization (+/-30 days) and underlying disease and/or stratum.

Patient information was obtained through two sources: a) Review of written hospital medical records (underlying diseases, alcohol consumption, and history of pneumonia and vaccination status) and b) Interview of the patient or close relatives (spouse or offspring) for visits to the doctor in the past year, alcohol consumption and vaccination status using a questionnaire

**Table 6.** Distribution of cases and controls by stratum.

<b>Stratum I</b>	<b>Stratum II</b>	<b>Stratum III</b>
<b>Solid organ neoplasia</b>	<b>COPD*</b>	<b>Patient not included on stratum I/ II.</b>
<b>Hematologic neoplasia</b>	<b>Diabetes mellitus</b>	
<b>Solid organ o bone marrow transplant</b>	<b>Heart failure grade 3 or 4</b>	
<b>Immunosuppressive therapy</b>	<b>Chronic renal failure</b>	
<b>Radiotherapy</b>	<b>Chronic liver disease</b>	
<b>Corticosteroid therapy (20 mg/d/15 day)</b>	<b>Asymptomatic infection HIV</b>	
<b>Autoimmune disease</b>		
<b>Asplenia</b>		
<b>Chronic renal failure requiring hemodialysis</b>		
<b>AIDS**</b>		
<b>Disabling neurologic disease</b>		

\*COPD: Chronic obstructive pulmonary disease.

\*\* AIDS: Acquired immunodeficiency syndrome.



completed by qualified staff. Vaccination status was also obtained from the vaccination card and health care centre vaccination registers.

The vaccination status was ascertained by staff blinded as to whether the patient was a case or control.

Patients were considered vaccinated when the vaccine had been given  $\geq 15$  days before the onset of pneumonia for cases or  $\geq 15$  days before the date of hospitalization for controls. The same criteria were used to determine prior influenza vaccination (IV) status.

We calculated the minimum required sample size according to Schlesselman criteria [51].

We assumed a prevalence of vaccination in the control group of 0.35 [52] and vaccine effectiveness (VE) against all-cause pneumonia of 35 %. With an alpha error of 0.05 (two-tailed), a beta error of 0.20 and three controls per case, we calculated that 269 cases and 807 controls would be needed. Because vaccination coverage was estimated to be lower in some of the participating regions, we increased the number of cases to 405 and controls to 1,215. The study was approved by the ethic committee of each hospital.

## Statistical Analysis

The differences observed between cases and controls according to the study variables were analysed using paired tests. The McNemar chi square test or binomial distribution test, when appropriate, was used for categorical variables and the paired t-test for continuous variables. A two-tailed distribution for all p values and considered  $p < 0.05$  to be statistically significant was assumed.

Conditional logistic regression (CLR) to account for the effects of confounding variables was used. The variables introduced in the CLR analysis were influenza vaccine status, variables potentially related to the vaccination response and those with a p value  $< 0.1$  in the univariate analysis. In the final analysis, variables with a significance of  $p < 0.05$  were included in the model. Adjusted odds ratios (ORs) for immunosuppressed (stratum I) and immunocompetent patients (stratum II and III) separately and for all three strata combined were calculated.

VE was estimated using the formula  $VE = (1 - OR) \times 100$ .

The statistical analysis was performed using the SPSS v15.0 statistical program.

## 2. Results

489 cases and 1,467 controls were included in the analysis; of 489 sets: 200 (41%) in stratum I, 190 (39%) in stratum II and 99 (20%) in stratum III.

The distribution of study variables was similar in the two groups, although more cases than controls had had a previous episode of pneumonia [119 (25.3%) vs 192 (13.7);  $p < 0.001$ ]. The only significant differences in the distribution of underlying diseases between cases and the three controls were in the proportions with solid organ neoplasia [51 (10.4%) in cases vs 304 (20.7%) in controls;  $p < 0.001$ ], hematologic neoplasia [43 (8.8%) vs 53 (3.6%);  $p < 0.001$ ], chronic obstructive pulmonary disease (COPD) [180 (36.8%) vs 442 (30.1%);  $p = 0.006$ ]; diabetes mellitus [108 (22.1%) vs 393 (26.8%);  $p = 0.04$ ] and corticosteroid therapy [24 (4.9%) vs 37 (2.5%);  $p = 0.009$ ] showed significant differences between cases and controls.

Of 489 sets, 200 were immunosuppressed and 289 immunocompetent.

### Vaccination effectiveness

The unadjusted and adjusted VE according to immune status are shown in Table 7. The overall adjusted VE for all three strata combined was 23.6% (95% CI: 0.9 to 41.0). For overall VE the significant variables included finally in the model were history of pneumonia, solid organ neoplasia, hematologic neoplasia, chronic obstructive pulmonary disease and diabetes mellitus.

**Table 7.** Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing hospitalization for pneumonia [49].

Group	n	Vaccinated	Unadjusted Analysis		Adjusted Analysis <sup>#</sup>	
			OR (95% CI)	VE % (95% CI)	OR (95% CI)	VE % (95% CI)
<b>Overall</b>						
Cases	489	229 (46.8)	1.0	--	1.0	--
Controls	1,467	750 (51.1)	0.795 (0.628-1.007)	20.5 (-0.7-37.2)	0.764 (0.590-0.991)	23.6 (0.9-41.0)
<b>Immunosuppressed</b>						
Cases	200	99 (49.5)	1.0	--	1.0	--
Controls	681	327 (54.5)	0.793 (0.561-1.119)	20.7 (-11.8-43.9)	0.790 (0.525-1.187)	21.0 (-18.7-47.5)
<b>Immunocompetent<sup>*</sup></b>						
Cases	289	130 (45.0)	1.0	--	1.0	--
Controls	867	423 (48.8)	0.797 (0.576-1.102)	20.3 (-10.2- 42.4)	0.764 (0.544-1.072)	23.6 (-7.2-45.6)

Data are presented as n, n(%) or % unless otherwise stated.

OR: Odds ratio. VE: vaccination effectiveness. CI: confidence interval

<sup>\*</sup>Strata II and III combined.

<sup>#</sup>For overall effectiveness, we adjusted for history of pneumonia, solid organ neoplasia, hematologic neoplasia, chronic obstructive pulmonary disease and diabetes mellitus.

For immunosuppressed patients, we adjusted for history of pneumonia, solid organ neoplasia, hematologic neoplasia, and chronic obstructive pulmonary disease.

For immunocompetent patients, we adjusted for history of pneumonia, diabetes mellitus and tobacco use.

The adjusted VE for immunosuppressed cases was 21.0% (95% CI: -18.7 to 47.5). For immunosuppressed patients, the significant variables included in the model were history of pneumonia, solid organ neoplasia, hematologic neoplasia, and chronic obstructive pulmonary disease.

When strata II and III were combined into one group of immunocompetent patients, the adjusted VE was 23.6% (95% CI: -7.2 to 45.6). For immunocompetent patients, the significant variables included in the model were a history of pneumonia, diabetes mellitus and smoking.

### 3. Discussion of results

We studied the effectiveness of the PPV-23 in preventing CAP requiring hospitalization and found an effectiveness of 23.6% (95% CI: 0.9% to 41.0%).

Before a vaccine is licensed, its clinical efficacy is evaluated in randomized clinical trials [52]. Once licensed for general use, the vaccination effectiveness can be assessed in observational studies, which are necessary when clinical trials have not provided conclusive results or have not been made in the population group for which the vaccine is recommended.

The 13-valent pneumococcal polysaccharide vaccine, the forerunner of the PPV-23 was evaluated in randomized clinical trials including young adult South-African miners [41], and the results encouraged research on its effectiveness in the population groups for which it was recommended: people aged  $\geq 65$  years and those with underlying disease of risk. The results of clinical trials in these groups were mostly inconclusive [53-57], suggesting that people susceptible to infection may not have an adequate immune response to the pneumococcal vaccine evaluated.

However, Fedson *et al.* showed that these studies did not have a sample size large enough to obtain conclusive results [42], and pointed out that the outcomes assessed in these studies were not always the correct ones. They recommended that two outcomes should be assessed in evaluations of the effectiveness of the PPV-23: invasive pneumococcal disease (pneumococcal bacteremia) or all-cause pneumonia, while other outcomes that have been studied, such as pneumococcal pneumonia, lower respiratory tract infections, pneumonia-related deaths and all-cause mortality not being acceptable [42]. This approach is based on the lack of diagnostic methods with sufficient sensitivity and specificity to correctly identify non-bacteremic pneumococcal pneumonia.

The current consensus is that observational studies have demonstrated the effectiveness of the PPV-23 in preventing invasive pneumococcal disease [42, 46, 47]. However, vaccination coverages in some countries are not high, partly due to doubts about the efficacy of the PPV-23 and its effectiveness in preventing non-bacteremic pneumococcal pneumonia [42, 46, 47, 58].

Our results show that the effectiveness of the PPV-23 in preventing hospitalization for pneumonia was 23.6% (95% CI: 0.9% to 41.0%).

Although the evidence is limited, some observational studies have shown some protective effect of the PPV-23 against hospitalization for CAP (Table 8). Nichol *et al.* [59, 60] and Wagner *et al.* [61] found that vaccination reduced hospital admissions due to all-cause CAP, and reduced the all-cause pneumonia case-fatality rate. Nichol *et al.* carried out a retrospective cohort study [59] which included 1,898 patients aged  $\geq 65$  years with COPD, and found that patients vaccinated with PPV-23 had a lower associated risk of hospitalization for CAP [relative risk (RR)= 0.57 (95% CI: 0.38 to 0.84)] and a lower risk of death from all causes [RR=0.71 (95% CI: 0.56 to 0.91)]. Wagner *et al.* [61] performed a case-control study of 1,077 residents in a geriatric hospital and found a significant reduction in the risk of pneumonia in people who received the PPV-23 [OR = 0.28,  $p < 0.001$ ] and a significant reduction in the risk of death from all causes [OR = 0.27,  $p < 0.001$ ] and death due to pneumonia [OR = 0.33,  $p < 0.001$ ]. Vila-Córcoles *et al.* [62] in a prospective cohort study of 11,241 subjects, confirmed the protection obtained by vaccination with PPV-23 against hospitalization for all-cause pneumonia [HR: 0.74 (95% CI: 0.59 to 0.92)] and against death from pneumonia [HR: 0.41 (95% CI: 0.23 to 0.72)].

However, Jackson *et al.* [63] in a retrospective cohort study of 47,365 people aged  $\geq 65$  years between 1998 and 2001, found no reduction in hospitalizations due to all-cause CAP [VE= -14% (95% CI: -28% to -2%)] despite finding a significant reduction in pneumococcal bacteremia [VE= 54% (95% CI: 13% to 76%)] and all-cause mortality [VE= 12% (95% CI: 5% to 17%)] in the 38,207 immunocompetent patients.

Likewise, neither Ansaldi *et al.* [64] or Skull *et al.* [65] found a reduction in hospitalizations due to CAP in patients vaccinated with the PPV-23. Ansaldi *et al.* [64] retrospectively studied 9,170 subjects of all ages (85.4% aged  $\geq 64$  years) for a period of 547,139 person-months, of which 71.7% were before and 28.3% after vaccination. They found that, in unvaccinated patients, the risk of hospitalization for asthma or otitis media was significantly higher, but that although risk of hospitalization for pneumonia was somewhat higher in people not vaccinated with PPV-23 (8.8 % in unvaccinated *versus* 7.8% in vaccinated subjects), the differences were not statistically significant [RR=1.12 (95% CI:0.91 to 1.38)].

Skull *et al.* [65] evaluated the effectiveness of the PPV-23 in preventing hospitalization for CAP in a case-cohort study of patients with a mean age of 78.4 years, but did not find that vaccination provided any benefits [RR= 0.99 (95% CI: 0.82 to 1.19)].

In our study, the effectiveness of PPV-23 in preventing hospitalization for pneumonia [23.6% (95% CI: 0.9% to 41.0%)] was close to that found by Vila-Córcoles *et al.* [26% (95% CI: 8% to 41%)] [62] and Nichol *et al.* [27% (CI: 95% -13% to 52%)], although in the latter study, the results were not statistically significant [60]. The VE in our study was lower than that found by Wagner *et al.* (72.1%) [61].

**Table 8.** Observational studies about PPV-23 effectiveness.

Author, year, place	Type of study	Patients	Number of subjects	Outcome studied	Vaccine effectiveness % (95% CI)
Nichol, 1999, USA [59]	Retrospective cohorts (2 years)	≥ 65 years with COPD*	1,898	Hospitalization for all-cause pneumonia	43% (16-62)
				Death due to all cause	29% (9-44)
Wagner, 2003, Vienna [61]	Cases-controls (2 years)	Residents in a geriatric hospital >70 years	359 cases 718 controls	All-cause pneumonia	72% p<0.0001
				Death due to all cause	73%
				Death due to pneumonia	67%
Vila-Córcoles, 2006, Tarragona [62]	Prospective cohorts (3 years)	Residents ≥ 65 years assigned to 8 CAP	11,241	Hospitalization for all-cause pneumonia	26% (8-41)

\*Chronic obstructive pulmonary disease.

A recently published meta-analysis of randomized clinical studies in older people failed to demonstrate protection of PPV-23 vaccination against all-cause pneumonia [66]. The study evaluated the efficacy of the PPV-23 in the prevention of certain clinical outcomes, including all-cause pneumonia. It also assessed the methodological quality of the trials analyzed. This meta-analysis included 22 trials of which the current PPV-23 was only evaluated in 8. Prevention of all-cause pneumonia was investigated in 19 trials, reducing to 11 who were studied in elderly patients or with chronic lung disease. The meta-analysis results for these 11 trials showed a RR = 0.89 (95% CI: 0.69 to 1.14), but these trials did not specify in which assessed the PPV-23, (and only in 8 of the 22 trials analyzed was the PPV-23 used in the study). According to information provided, it appears that only 5 of the 11 evaluated the PPV-23.

A 2008 systematic Cochrane review [67] of English-language studies evaluating the efficacy and effectiveness of the PPV-23 included 15 randomized trials and 7 observational studies. The observational studies provided evidence of protection against invasive pneumococcal disease in populations where the PPV-23 is usually used [OR= 0.48 (95% CI: 0.37 to 0.61)]. The meta-analysis of the clinical trials also showed the PPV-23 provided protection against invasive pneumococcal disease [OR= 0.26 (95% CI: 0.15 to 0.46)]. The effectiveness of the PPV-23 against all-cause pneumonia was not proven because, although the OR was significant [OR = 0.71 (95% CI: 0.52 to 0.97)] with a VE of 29% [95% CI: 3% to 48%], the meta-analysis had substantial statistical heterogeneity. The PPV-23 was associated with a not significant reduction in all-cause mortality [OR = 0.87 (95% CI: 0.69 to 1.10)].

Our study found an effectiveness of the PPV-23 in preventing hospitalization for all-cause CAP of 23.6%. It is estimated that only 30-50% of cases of CAP are due to *S. pneumoniae* [25] and therefore the effectiveness of the PPV-23 against pneumococcal pneumonia (bacteremic and non-bacteremic) would be expected to be higher. In the study by Austrian *et al.* [41] carried out in South African miners with the 13-valent pneumococcal polysaccharide vaccine, the VE was 82% against bacteremic pneumococcal pneumonia and 78.5% against pneumococcal pneumonia (diagnosed by sputum and blood cultures). Observational studies have shown that the PPV-23 prevents 50-70% of cases of invasive pneumococcal disease (due to all serotypes) [25, 42]. If 30-50% of all cases of CAP in our population are caused by *S. pneumoniae*, our findings suggest that if the level of protection against all-cause CAP was 23.6%, the level of protection against pneumococcal pneumonia would be near the level of protection (50-70%) found in observational studies of invasive pneumococcal disease [46].

Our study, like other observational studies, has strengths and limitations. One strength was the size of the sample (489 cases and 1,467 controls), which yielded statistically significant results for the overall study population. The adjusted overall VE was 23.6% (95% CI: 0.9% to 41.0%). The lack of statistical significance in immunocompetent patients may be due to a sample size that was not sufficient to study the effectiveness of groups according to the immune status.

In case-control studies of vaccination there is always a possibility of bias that distorts the results and reduces the validity of the findings [68]. One source of bias is the assessment of vaccination status in patients. However, in our study, information on the vaccination status was obtained retrospectively by investigators who were unaware of whether the patient was a case or a control, using the records of the same primary care centres for cases and

controls, and therefore this point is moot. Moreover, the vaccination status was investigated in all primary care centres to which the patient was assigned since the PPV-23 was introduced in the vaccination programme (2000).

To control for confounding variables, controls were matched with cases by date of hospitalization, age, sex and underlying diseases that could influence the disease incidence. Even so, statistically significant differences between cases and controls were observed for some variables: history of pneumonia, solid organ malignancy, hematologic malignancy, corticosteroid treatment, diabetes mellitus and COPD. The explanation is that pairing was carried out taking into account the disease with greater immunosuppression or the longest evolution, but many patients had more than one disease. To avoid the possible confounding effect of these variables, we adjusted the results using conditional logistic regression. Influenza vaccination could have a confounding effect when assessing the protective effect of the vaccine. However, we believe that this possibility was minimized as the variable was always introduced into the conditional logistic regression analysis.

#### **4. Conclusion**

The incidence of CAP is always greater in the elderly and persons with underlying diseases, and between 30 and 50% of cases of CAP requiring hospitalization are caused by *S. pneumoniae*. Therefore the reduction of pneumonia-related morbidity partially will depend on the improved use of preventive strategies such as immunization against *S. pneumoniae*.

In our study, the overall effectiveness of the PPV-23 in preventing hospitalization for pneumonia is estimated at 23.6% (95% CI: 0.9% to 41.0%). Current recommendations on PPV-23 vaccination are based on studies of vaccine effectiveness against invasive pneumococcal disease. Our results suggest that the PPV-23 is effective and reduces hospital admissions due to pneumonia in the elderly, thereby reinforcing the application of vaccination programmes in this age group.

#### **Acknowledgements**

The authors are grateful to *European Respiratory Journal* for their permission to use some results that were published in the journal in 2010.

The authors are grateful to professor Guillem Prats for helpful suggestions to a previous version of the chapter.

The authors thank the other members of the Working Group for the Study of the prevention of CAP in the elderly: Jordi Carratalà and Adriana Manzur (Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat,

Spain), Jose-María Bayas and Silvia Sugañes (Hospital Clínic, Barcelona, Spain), Wenceslao Varona and Angel Terren (Hospital Royo Villanova, Zaragoza, Spain), Dolores Sousa, Susana Rivera, Isabel Justo and Ana Arevalo (Hospital Juan Canalejo, Coruña, Spain), Jose-Miguel Celorrio, Carmen García and Esperanza Clemente (Hospital Ernest Lluch, Calatayud, Spain), Manel Nebot, Xavier Sintès (Public Health Agency of Barcelona, Spain), Laura Ruiz and Joan Batalla [Department of Health, Generalitat of Catalonia and CIBER Epidemiología y Salud Pública (CIBERESP), Spain].

The authors thank all health centres that provided vaccination information on their patients. None received any economic compensation.

This study was funded by *Instituto de Salud Carlos III*, Madrid, Spain (Project numbers: 04/1835; 04/0151; 04/2516; 04/1573; 04/2303; 04/2351) and CIBER Epidemiología y Salud Pública (CIBERESP), PD07-006 and AGAUR (Grant number 2009/SGR42).

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