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Effectiveness of the Pneumococcal Polysaccharide Vaccine in Preventing Pneumonia in the Elderly.

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ABSTRACT

The objective of the study was to evaluate the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV) in preventing hospital admission for community-acquired pneumonia in people ≥ 65 years of age.

We conducted a matched case-control study in patients with community-acquired pneumonia admitted to five Spanish hospitals. Cases were persons aged ≥ 65 years admitted to hospital through the emergency department who presented a clinical and radiological pattern compatible with pneumonia using established criteria. We matched each case with three control subjects by sex, age (+/- 5 years), date of hospitalization (+/- 30 days) and underlying disease. The study period was 1 May 2005 to 31 January 2007. The PPV immunization status of cases and controls was investigated. Adjusted odds ratios for vaccination were calculated using logistic regression analysis.

A total of 489 cases and 1467 controls were included in the final analysis. The overall adjusted vaccination effectiveness for all patients was 23.6% [95% confidence interval (CI) 0.9-41.0]. The adjusted vaccination effectiveness for immunosuppressed patients was 21.0% (95% CI -18.7-47.5).

Our results suggest that the PPV may potentially reduce hospitalizations for pneumonia in the elderly and supports vaccination programs in this age group.

INTRODUCTION

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality in elderly people and those of any age with underlying diseases [1,2]. In Spain, the overall incidence in adults varies between 2 and 10 cases/1,000 persons/year in all ages and between 14 and 35/1,000 persons/year in persons aged > 70 years [3,4]. In a Spanish study, the incidence increased dramatically by age in elderly people (9.9/1,000 in people aged 65-74 years versus 29.4 in people aged ≥ 85 years) [4]. Hospitalizations due to CAP increase with age and may reach 61 to 67% in people aged > 65 years [5,6]. Case-fatality rates may reach 17% in patients aged > 75 years [4], with higher rates in those with underlying disease [1,3,5,6]. A substantial proportion of CAP cases requiring hospitalization are caused by *Streptococcus pneumoniae*: 30-50% according to most reports [1,7-11]. Bacteremic pneumococcal pneumonia, the most severe disease form, accounts for only 10-20% of adult cases of CAP caused by *S. pneumoniae,* with non-bacteremic pneumococcal pneumonia being much more frequent [1].

The 23-valent pneumococcal polysaccharide vaccine (PPV) has been available in the United States for 25 years and is currently licensed in most developed countries. Vaccination is usually recommended for people aged ≥ 65 years and for high-risk persons aged > 2 years [1,12-13]. There is a general consensus that observational studies have shown vaccination to be effective in preventing invasive pneumococcal disease [14-16]. However, vaccination rates are not high in most countries, partly due to doubts about the vaccine's efficacy and vaccination effectiveness in preventing non-bacteremic pneumococcal pneumonia [14-17].

Laboratory methods for diagnosing non-bacteremic pneumococcal pneumonia have a low sensitivity and specificity and are difficult to carry out in clinical practice. Therefore, all-cause pneumonia has been proposed as a more appropriate outcome measure for evaluating vaccination effectiveness (VE) [1,15]. If a substantial proportion of hospital admissions for CAP are of pneumococcal origin and vaccination is effective against non-bacteremic and bacteremic disease, this should be reflected in a decline in admissions for all-cause pneumonia.

In 1999, pneumococcal vaccination programs for the elderly and high-risk individuals were introduced in several Spanish regions [12] according to international recommendations [13]. Vaccination coverage in some regions reached 35% in 2002 and the current level is > 60%. This high coverage [18] and the large number of hospitalizations for CAP in Spain facilitated the objective of this study: To evaluate the effectiveness of PPV in preventing hospital admission for CAP in people aged > 65 years by assessing whether the proportion of vaccinated subjects was lower in hospitalized patients with pneumonia than in those without pneumonia.

METHODS

Study Design

We conducted a matched case-control study in patients with CAP admitted to five hospitals in three Spanish regions. The study period was 1 May 2005 to 31 January 2007.

Case selection

We defined a case as a person aged ≥ 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 > 38ºC, hypothermia < 35ºC or dyspnea within the past 24 hours [1,5,10]. Exclusion criteria were institutionalized patients, patients with nosocomial pneumonia (onset ≥ 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.

Selection of controls

We selected three hospital controls for each case: two medical patients and one surgical patient. Controls aged ≥ 65 years admitted through the emergency department with a diagnosis other than pneumonia were 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.

Demographic and other variables

For each case and control we obtained information on age, sex, dates of hospitalization and discharge (alive or dead), smoking, risk-consumption of alcohol and the presence or absence of underlying diseases or conditions. We stratified each case 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 - solid organ or hematologic neoplasia with activity in the past year, solid organ or bone marrow transplant, radiotherapy within the past 3 months, immunosuppressive therapy or treatment with corticosteroids $\geq$ 20 mg daily in the past month, asplenia, autoimmune disease, chronic renal failure requiring hemodialysis, active nephrotic syndrome and acquired immunodeficiency syndrome (AIDS). We also included those with neurological disease impeding daily activities. Stratum II (moderate risk) included immunocompetent patients with one or more high-risk medical conditions - heart failure grade 3 or 4, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic renal failure not requiring hemodialysis, and chronic liver disease. Stratum III included patients not included in strata I or II.

To guarantee the true value of the overall effectiveness of vaccination in preventing all-cause pneumonia hospitalization, the numbers of cases in the three strata were selected to reflect the real proportions of the corresponding strata in hospitalizations for all-cause pneumonia in Catalonia (Dr. Carratalá, personal communication). When the number of subjects required for each stratum was reached, recruitment for this stratum was stopped.

Matching cases and controls

We matched each case with three control subjects by sex, age (+/- 5 years), date of hospitalization (+/- 30 days) and underlying disease. If the case had more than one high-risk medical condition and was immunosuppressed (stratum I), control subjects were matched using the immunosuppressive disease of greatest duration (if recorded) or another immunosuppressive condition suffered by the case, if disease duration was not available. If controls with the same underlying disease were not found, we sought controls with diseases from the same stratum.

If the case had more than one high-risk medical condition but was not immunosuppressed (stratum II), controls were matched using the disease of greatest duration (if recorded) or by some other condition of risk of the case if information on duration was not available.

If the case had no high-risk condition (stratum III), we selected controls with no such conditions. If no adequate controls were found, the intervals for age and the date of hospitalization of the case were extended.

Information Collection

Patient information was obtained through two sources: a) Review of written hospital medical records (underlying diseases, alcohol consumption, 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 completed by qualified staff. Vaccination status was also obtained from the vaccination card and health care centre vaccination registers.

Ascertainment of pneumococcal and influenza vaccination status

We sought information on the vaccination status in all health centres each patient had visited during the five years before hospitalization. The vaccination status was ascertained by staff blinded as to whether the patient was a case or control. As vaccination status may be recorded in different documents, we searched all relevant sources and considered PPV as administered only when confirmed by the patient's hospital record, adult vaccination card or primary health care vaccination record. Patients were considered vaccinated when the vaccine had been given ≥ 15 days before the onset of pneumonia for cases or ≥ 15 days before the date of hospitalization for controls**.** The same criteria were used to determine prior influenza vaccination (IV) status.

Sample Size

We calculated the minimum required sample size according to standard criteria [19]. We assumed a prevalence of vaccination in the control group of 0.35 [20] and 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 1215.

Statistical Analysis

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

We used conditional logistic regression (CLR) to account for the effects of confounding variables. 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. We calculated adjusted odds ratios (ORs) for immunosuppressed (strata I) and immunocompetent patients (stratum II and III) separately and for all three strata combined.

VE was estimated using the formula VE = (1-OR) x 100.

The study was approved by the ethics committee of each participating hospital.

RESULTS

Recruitment of Cases and Controls

Of the 598 cases recruited, 35 (5.9%) were excluded because their vaccination status (PPV or IV) could not be determined. We recruited 1605 controls, of which the PPV or IV status could not be determined in 38 (2.4%).

Of the 563 cases in whom vaccination status was determined, three appropriate controls were not found for 58. Of the remaining 505 complete sets, 16 were excluded because one or more control subject exceeded the age interval by more than eight years. Therefore, 489 complete sets were included in the final analysis: 200 (41%) in stratum I, 190 (39%) in stratum II and 99 (20%) in stratum III.

Characteristics of Study Subjects

The characteristics of cases and controls for all patients are shown in table 1. The distribution of study variables was similar in the two groups, although more cases than controls had had a previous episode of pneumonia. The only significant differences in the distribution of underlying diseases between cases and the three controls were in the proportions with solid organ and hematologic neoplasia and COPD; diabetes mellitus and corticosteroid therapy showed significant differences between cases and two of the controls.

Of 489 sets, 200 were immunosuppressed and 289 immunocompetent. The characteristics of cases and controls according to immune status are also shown in table 2.

Vaccination Effectiveness

The history of pneumococcal vaccination in cases and controls, the unadjusted and adjusted ORs and the unadjusted and adjusted VE according to immune status are shown in table 3. The overall adjusted VE for all three strata combined was 23.6% (95% CI 0.9-41.0). For overall effectiveness the significant variables included finally in the model were history of pneumonia, solid organ neoplasia, hematologic neoplasia, chronic obstructive pulmonary disease and diabetes mellitus. The adjusted VE for immunosuppressed cases was 21.0% (95% CI -18.7-47.5). 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 -7.2-45.6). For immunocompetent patients, the significant variables included in the model were a history of pneumonia, diabetes mellitus and smoking.

DISCUSSION

We have found that the PPV has an effectiveness in preventing hospitalizations due to pneumonia of 23.6% (0.9-41.0). Although evidence is limited, some observational studies have shown a protective effect of PPV against hospitalization for CAP. NICHOL *et al*. [21,22] and WAGNER *et al*. [23] found that vaccination reduced hospital admissions for all-cause pneumonia. Protection was observed both against cases of disease and against deaths from all-cause pneumonia [22, 23]. Protection against pneumonia was also confirmed by a prospective cohort study by VILA-CÓRCOLES *et al*. [24]. However, JACKSON *et al.* [25] found no reduction in hospitalization for pneumonia, despite finding significant reductions in immunocompetent patients in the occurrence of both pneumococcal bacteremia (54%) and all-cause mortality (12%) [26]. A historical cohort study by ANSALDI *et al*. [27] and a case-cohort study by SKULL *et al.* [28] also failed to show that vaccination reduced hospital admission for CAP.

The effectiveness in preventing hospitalizations due to pneumonia (23.6%) in our study was close to that found by NICHOL *et al.* (27%) [22] and VILA-CÓRCOLES *et al.* (26%) [24] but lower than that found by WAGNER *et al.* in a study carried out in a long-stay geriatric hospital (72.1%) [23].

A recently published meta-analysis of randomized clinical trials carried out in elderly population fail to show protection of 23-valent pneumococcal vaccine against all cause pneumonia [29]. The Cochrane foundation has recently published a systematic review [30] of English-language studies evaluating the efficacy and effectiveness of the 23-valent pneumococcal vaccine. The review evaluated the effectiveness of the vaccine in reducing all cause mortality but not the prevention of hospitalizations due to pneumonia. The authors also reviewed the results of clinical assay designed to evaluate the efficacy of the vaccine in preventing all cause pneumonia, and found a global result of 29% (95% CI 3-48), similar to the results of our study (23.6%: 95% CI:0.9-4). Only 30-50% of cases of CAP are thought to be due to *S. pneumoniae* [1], and thus the effectiveness of PPV against all cases of pneumococcal pneumonia (non-bacteremic and bacteremic) would be expected to be much higher. In the study by Austrian of a 13-valent pneumococcal polysaccharide vaccine in South African gold miners, vaccine efficacy was 82% against bacteremic pneumococcal pneumonia and 78.5 % against putative (bacteremic and sputum culture-positive) pneumococcal pneumonia caused by vaccine serotypes[31]. Observational studies have shown that pneumococcal vaccination prevents approximately 50% to 70% of hospitalizations for invasive pneumococcal disease (all serotypes) [1,15]. If 30% to 50% of all cases of CAP in our population were caused by vaccine-type *S. pneumoniae*, our findings suggest that if the level of vaccination-induced protection against all CAP cases was 23.6% (Table 2), the level of protection against vaccine-serotype pneumococcal pneumonia was close to the level of protection (50% to 70%) found in observational studies of invasive disease alone [16].

Some studies suggest that the PPV reduces rates of intensive care unit (ICU) admission and in-hospital CAP mortality [32-34]. Moreover, even if the proportion of non-bacteremic pneumococcal pneumonia admissions prevented by vaccination were much lower than suggested by our results, preventing these additional hospital admissions and reducing ICU admissions and in-hospital CAP mortality would still dramatically increase the cost-effectiveness of a vaccine that is already very cost-effective in preventing invasive disease alone [35].

Our study, like other observational epidemiological studies, has strengths and limitations. One strength was the large sample size (489 cases and 1,467 controls), which allowed statistically significant results to be obtained for the whole population studied. The overall adjusted VE (all cases and controls) was 23.6% (95% CI 0.9-41.0). The lack of significance in immunocompetent subjects may be due to the small sample size of this group.

In case-control studies of vaccination there is always the possibility that bias can distort the results and decrease the validity of the findings [36]. One source of bias is incomplete or inaccurate ascertainment of the vaccination status. This did not occur in our study because information on vaccination status was obtained retrospectively by blinded investigators using common records for both cases and controls, and these records were completed before the study period began.

To control for confounding variables, controls were matched with cases for sociodemographic and medical variables (risk factors) that could have influenced disease incidence. Even so, statistically significant differences between cases and controls were observed for six medical variables (history of pneumonia, solid organ neoplasia, hematologic neoplasia, corticosteroid therapy, diabetes mellitus and COPD). We adjusted for the possible confounding effect of these variables using conditional logistic regression. Influenza vaccination could have been a possible confounding factor, although we believe it had no effect because the variable was introduced into the conditional logistic regression analysis and because the proportion of vaccinated cases and controls was similar.

Introduction of the seven-valent conjugated vaccine in children aged < 2years in the first decade of this century does not seem to have caused any bias. In the United States, the incidence of invasive pneumococcal disease in the elderly has fallen since conjugate vaccination programs were introduced. This is largely because reduced rates of nasopharyngeal colonization by vaccine serotypes in children have reduced rates of transmission to older individuals [37-39]. In Spain, the 7-valent conjugated pneumococcal vaccine has not been included in the official routine vaccination schedules of the Ministry of Health or those of the three Regions participating in this study. Nonetheless, it is estimated that vaccination coverage with the conjugated vaccine in Spain during the period of this study was between 30% and 40% [40,41]. In the US, rates of invasive disease in adults began to fall soon after conjugate vaccination of children was introduced, although vaccination rates were low and within the range of those reported in Spain [37,38]. It is conceivable that conjugate vaccination of children in Spain had already reduced absolute rates of invasive pneumococcal disease in older adults. Nevertheless, the relative reduction in rates of CAP observed in our study can be considered to have occurred independently of the effects of conjugate vaccination of children. The only effect conjugate vaccination of children might have had on our estimate of effectiveness (i.e., relative risk reduction) of PPV in older adults would have been to reduce overall rates of CAP, thus leading to a requirement for larger sample sizes to detect an effect of the polysaccharide vaccine.

Current recommendations for PPV vaccination are based on studies of vaccination effectiveness against invasive pneumococcal disease. Our results reinforce these recommendations and suggest that the cost effectiveness of PPV is greater than reported, since all economic studies of PPV carried out until the present have only considered its protective value against invasive pneumococcal disease.

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Statement of interest

All authors state they have no conflict of interest.

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TABLE 1. Characteristics of Cases and Controls for All Patients.

	All patients*						
	Cases n=489	**Control 1** n=489	**p- value**#	**Control 2** n=489	**p- value**¶	**Control 3** n=489	**p- value** +
Age (years)	77.2±6.7	77.1±6.3	0.388	77.3±6.4	0.489	76.6±6.2	0.001
History of pneumonia	119 (25.3)	76(16,3)	0.001	74 (15,7)	<0.001	42 (9.0%)	<0.001
Influenza vaccination	306 (62.6)	322 (65.8)	0.258	320 (65.4)	0.340	325 (66.5)	0.202
Pneumococcal vaccination	229 (46.8)	258 (52.8)	0.037	243 (49.7)	0.307	249 (50.9)	0.161
Visited doctor in the past year	449 (93.0)	452 (92.8)	1.00	447 (92.2)	0.791	454 (93.4)	0.784
Time since vaccination (days)	1,548±664	1,436±694	0.048	1,502±698	0.642	1,447±719	0.026
Solid organ neoplasia	51 (10.4)	85 (17.4)	<0.001	90 (18.4)	<0.001	129 (26.4)	<0.001
Hematologic neoplasia	43 (8.8)	23 (4.7)	0.006	16 (3.3)	<0.001	14 (2.9)	<0.001
Solid organ transplant	3 (0.6)	3 (0.6)	1.00	1 (0.2)	0.625	3 (0.6)	1.00
Bone marrow transplant	2 (0.4)	1 (0.2)	1.00	1 (0.2)	1.00	0 (0.0)	0.500
Radiotherapy	4 (0.8)	5 (1.0)	1.00	3 (0.6)	1.00	2 (0.4)	0.688
Immunosuppressive therapy	18 (3.7)	10 (2.0)	0.115	14 (2.9)	0.571	12 (2.5)	0.307
Corticosteroid therapy	24 (4.9)	16 (3.3)	0.134	12 (2.5)	0.023	9 (1.8)	0.004
Splenectomy	4 (0.8)	4 (0.8)	1.00	1 (0.2)	0.375	5 (1.0)	1.00
Autoimmune disease	14 (2.9)	22 (4.5)	0.152	12 (2.5)	0.791	10 (2.0)	0.503
Chronic renal failure with dialysis	12 (2.5)	6 (1.2)	0.180	12 (2.5)	1.00	5 (1.0)	0.118
Disabling neurological disease	82 (16.8)	81 (16.6)	1.00	82 (16.8)	1.00	55 (11.2)	<0.001
Diabetes mellitus	108 (22.1)	135 (27.6)	0.013	123 (25.2)	0.184	135 (27.6)	0.009
Heart failure, grade 3 or 4	48 (9.8)	54 (11.0)	0.496	63 (12.9)	0.082	40 (8.2)	0.312
COPD	180 (36.8)	153 (31.3)	0.004	159 (32.5)	0.021	130 (26.6)	<0.001
Chronic liver disease	16 (3.3)	17 (3.5)	1.00	16 (3.3)	1.00	9 (1.8)	0.167
Renal failure, no dialysis	22 (4.5)	37 (7.6)	0.041	27 (5.5)	0.551	16 (3.3)	0.405
Chronic alcoholism	40 (9.3)	31 (7.2)	0.203	40 (9.5)	0.779	29 (7.0)	0.243
Smoker or Ex-smoker	267 (54.9)	251 (51.6)	0.136	250 (51.3)	0.139	239 (49.1)	0.015

Data are presented as n (%) or mean ± SD unless otherwise stated.

COPD: chronic obstructive pulmonary disease, SD: Standard Deviation.

*Strata I, II and III combined. # Comparing between cases and control 1. ¶ Comparing between cases and control 2. + Comparing between cases and control 3.

TABLE 2. Characteristics of Cases and Controls according to Immune Status.

Immunocompetent patients *	Cases n=289	Control 1 n=289	p- value[#]	Control 2 n=289	p- value[¶]	Control 3 n=289	p-value [+]
Age (years)	77.1±6.5	76.9±6.2	0.283	77.1±6.2	0.883	76.3±6.0	<0.001
History of pneumonia	67 (24.0)	59 (21.8)	0.450	50 (17.9)	0.054	30 (11.0)	<0.001
Influenza vaccination	188 (65.1)	208 (72.0)	0.055	200 (69.2)	0.281	199 (68.9)	0.367
Pneumococcal vaccination	130 (45.0)	145 (50.2)	0.147	135 (46.7)	0.675	143 (49.5)	0.228
Visited doctor in the past year	266 (92.0)	262 (91.0)	0.749	265 (91.7)	1.00	271 (93.8)	0.472
Time since vaccination (days)	1,543±602	1,404±686	0.021	1,417±707	0.025	1,456±731	0.187
Diabetes mellitus	70 (24.2)	86 (29.8)	0.024	84 (29.1)	0.045	91 (31.5)	0.001
Heart failure, grade 3 or 4	38 (13.1)	43 (14.9)	0.499	50 (17.3)	0.097	31 (10.7)	0.281
COPD	126 (43.6)	124 (42.9)	0.832	131 (45.3)	0.383	114 (39.4)	0.038
Chronic liver disease	8 (2.8)	5 (1.7)	0.508	7 (2.4)	1.00	6 (2.1)	0.754
Renal failure, no dialysis	11 (3.8)	17 (5.9)	0.263	17 (5.9)	0.307	10 (3.5)	1.00
Chronic alcoholism	234 (89.7)	242 (92.7)	0.296	229 (91.2)	1.00	16 (6.3)	1.00
Smoker or Ex-smoker	172 (59.5)	153 (53.1)	0.033	154 (53.5)	0.036	145 (50.3)	0.003
Immunosuppressed patients	**Cases** n=200	**Control 1** n=200	**p-value**[#]	**Control 2** n=200	**p-value**[¶]	**Control 3** n=200	**p-value** [+]
Age (years)	77.4±7.1	77.3±6.4	0.956	77.6±6.6	0.347	77.2±6.3	0.457
History of pneumonia	52 (27.1)	17 (8.8)	0.001	24 (12.6)	0.001	12 (6.1)	<0.001
Influenza vaccination	118 (59.0)	114 (57.0)	0.734	120 (60.0)	0.912	126 (63.0)	0.422
Pneumococcal vaccination	99 (49.5)	113 (56.5)	0.166	108 (54.0)	0.342	106 (53.0)	0.515
Visited doctor in the past year	183 (94.3)	190 (95.5)	0.791	182 (92.9)	0.839	183 (92.9)	0.832
Time since vaccination (days)	1,556±742	1,475±705	0.628	1,608±676	0.133	1,435±706	0.063
Solid organ neoplasia	51 (25.5)	85 (42.5)	<0.001	90 (45.0)	<0.001	129 (64.5)	<0.001
Hematologic neoplasia	43 (21.5)	23 (11.5)	0.006	16 (8.0)	<0.001	14 (7.0)	<0.001
Solid organ transplant	3 (1.5)	3 (1.5)	1.00	1 (0.5)	0.625	3 (1.5)	1.00
Bone marrow transplant	2 (1.0)	1 (0.5)	1.00	1 (0.5)	1.00	0 (0.0)	0.500
Radiotherapy	4 (2.0)	5 (2.5)	1.00	3 (1.5)	1.00	2 (1.0)	0.688
Immunosuppressive therapy	18 (9.0)	10 (5.0)	0.115	14 (7.0)	0.571	12 (6.0)	0.307
Corticosteroid therapy	24 (12.0)	16 (8.0)	0.134	12 (6.0)	0.023	9 (4.5)	0.004
Splenectomy	4 (2.0)	4 (2.0)	1.00	1 (0.5)	0.375	5 (2.5)	1.00
Autoimmune disease	14 (7.0)	22 (11.0)	0.152	12 (6.0)	0.791	10 (5.0)	0.503
Chronic renal failure with dialysis	12 (6.0)	6 (3.0)	0.180	12 (6.0)	1.00	5 (2.5)	0.118
Disabling neurological disease	81 (40.5)	81 (40.5)	1.00	82 (41.0)	1.00	55 (27.5)	0.001
Diabetes mellitus	38 (19.0)	49 (24.5)	0.215	39 (19.5)	1.00	44 (22.0)	0.525
Heart failure, grade 3 or 4	10 (5.0)	11 (5.5)	1.00	13 (6.5)	0.664	9 (4.5)	1.00
COPD	54 (27.0)	29 (14.5)	0.002	28 (14.0)	0.001	16 (8.0)	0<0.001
Chronic liver disease	8 (4.0)	12 (6.0)	0.503	9 (4.5)	1.00	3 (1.5)	0.180
Renal failure, no dialysis	11 (5.5)	20 (10.0)	0.124	10 (5.0)	1.00	6 (3.0)	0.332
Chronic alcoholism	13 (7.7)	12 (7.0)	0.629	18 (10.6)	0.678	13 (7.9)	1.00
Smoker or Ex-smoker	95 (48.2)	98 (49.5)	0.880	96 (48.2)	1.00	94 (47.2)	0.890

Data are presented as n (%) or mean ± SD unless otherwise stated.

COPD: chronic obstructive pulmonary disease, SD: Standard Deviation.

*Strata II and III combined. # Comparing between cases and control 1. ¶ Comparing between cases and control 2. + Comparing between cases and control 3.

TABLE 3. Effectiveness of 23-Valent Pneumococcal Polysaccharide Vaccination in Preventing Hospitalization for Pneumonia

			Unadjusted Analysis		**Adjusted Analysis**[#]	
Group	**n**	**Vaccinated**	**OR (95% CI)**	**VE %(95% CI)**	**OR (95% CI)**	**VE %(95% CI)**
Overall						
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)
Immunosuppressed						
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)
Immunocompetent[*]						
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
[*]Strata II and III combined.
[#] 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.