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RESEARCH PAPER

Risk of hospitalization due to pneumococcal disease in adults in Spain. The CORIENNE study

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ABSTRACT

Pneumococcal disease causes a high burden of disease in adults, leading to high rates of hospitalization, especially in the elderly.

All hospital discharges for pneumococcal disease and pneumococcal pneumonia among adults over 18 y of age reported in first diagnostic position in 2011 (January 1, 2011 through December 31, 2011) were obtained.

A total of 10,861 hospital discharges due to pneumococcal disease were reported in adults in Spain in 2011 with an annual incidence of hospitalization of 0.285 (CI 95%: 0.280–0.291) per 1,000 population over 18 y old. Case-fatality rate was 8%. Estimated cost of these hospitalisations in 2011 was more than 57 million €.

Pneumococcal pneumonia accounted for the 92% of the hospital discharges All the chronic condition studied: asplenia, chronic respiratory disease, chronic heart disease, chronic renal disease, Diabetes Mellitus and immunosuppression, increased the risk of hospitalization in patients with pneumococcal pneumonia, especially in those aged 18–64 y old. Case-fatality rate among adult patients hospitalized with at least one underlying condition was significantly higher than among patients without comorbidities.

Our results identified asplenia, chronic respiratory disease, chronic heart disease, chronic renal disease, chronic liver disease, Diabetes Mellitus and immunosuppression as risk groups for hospitalization. Older adults, immunocompromised patients and immunocompetent patients with underlying conditions could benefit from vaccination.

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Introduction

In Europe, Community-Adquired Pneumonia (CAP) has an important impact in terms of morbidity and mortality in adults as well as in health care costs. *Streptococcus pneumoniae* is the leading bacterial cause of CAP requiring hospital admission and accounts for about 30% of the cases.[1]

Particularly in the elderly, Pneumococcal pneumonia is associated with a high risk of hospitalization.[2-4] The annual hospitalization rates due to pneumococcal pneumonia in Spain (2003–2007) was 1.09/1,000 among adults older than 50 years, reaching up to 4.21/1,000 in those 85 y of age and older.[5]

Despite the recognized importance of pneumococcal disease in adults, information on the true burden of the disease is not well known, as suggested by the fact that reported incidence and mortality rates in adult populations have varied importantly in the last 2 decades.[6] A recent study estimating the burden of pneumococcal pneumonia among adults showed that for every case of bacteremic pneumococcal pneumonia there are at least other 3 additional cases of non-bacteremic pneumococcal pneumonia.[7] In addition, it seems that the proportion of comorbid chronic diseases has increased in the last years,[6] but very little is known about how the presence of underlying conditions and/or age influence the disease burden due to pneumococcal pneumonia.

Among the efforts to prevent pneumonia are to reduce preventable comorbid conditions and to improve vaccine effectiveness and vaccination programs, particularly in elderly.[6] Currently, 3 vaccines that offer protection against pneumococcal disease are available in Spain: a 10-valent conjugate vaccine (PCV10) for children, a 13-valent conjugate vaccine (PCV13) for the entire population and a 23-valent polysaccharide vaccine (PPSV23) from age 2 onwards which is recommended particularly for adults older than the age of 65 y and for specific groups at risk of pneumonia. The Advisory Committee on Immunization Practices (ACIP) currently recommends that a dose of PCV13 be followed by a dose of PPSV23 in all adults aged ≥65 years who have not previously received pneumococcal vaccine and in persons aged ≥2 years who are at high risk for pneumococcal disease because of underlying medical conditions.[8]

The Spanish centralized hospital discharge database which covers almost all the Spanish population and includes more than 98% of admissions in hospitals of the national health care system, provides a complete record of all hospitalisations and, in general, is not subject to the limitations of outpatient surveillance systems, such as under-diagnosis or deficiencies in reporting. This database can give a reasonable approximation to the burden of pneumonia hospitalisation by age and has

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been used as a reliable tool for research purposes including epidemiological studies on pneumococcal disease and other infectious diseases.[9-12]

This epidemiological retrospective study was designed to provide population-based estimates of the burden of hospitalisation for pneumococcal disease in Spain and to identify relevant risk factors for pneumococcal pneumonia on a national level in order to guide recommendations for pneumococcal vaccination in adults.

Results

A total of 10,861 hospital discharges due to pneumococcal disease were reported in adults in Spain in 2011 corresponding to an annual incidence of hospitalization of 0.285 (CI 95%: 0.280–0.291) per 1,000 population over 18 y old. Mean age of the hospitalized patients was 0.708 (CI 95%: 0.702–0.718) years and 60% were males. There were 880 deaths among the hospitalized patients, with a case-fatality rate of 8%.

Pneumococcal pneumonia accounted for the 92% (n=9995) of the hospital discharges due to Pneumococcal disease in adults, corresponding to an annual incidence of hospitalization of 0.262 (CI 95%: 0.257–0.268) per 1,000. Case-fatality rate among these patients was 7%.

Table 1 shows hospitalization rate, mortality rate and case-fatality rate of pneumococcal disease by ICD-9CM code and group of age. Hospitalization rate and mortality rate were significantly higher for pneumococcal pneumonia than for pneumococcal septicemia and pneumococcal meningitis ($p<0.001$). On the other hand, case-fatality rate was significantly higher in pneumococcal septicemia and pneumococcal meningitis than in pneumococcal pneumonia ($p<0.001$). Of all the hospital discharges due to pneumococcal pneumonia in adults, 71% occurred in the elderly. This percentage decreased to 67% for pneumococcus infection in conditions classified elsewhere and of unspecified site (ICD 9-CM 041.2), to 57% for pneumococcal septicaemia and to 42% for pneumococcal meningitis.

Hospitalization rate, mortality rate and case-fatality rate were significantly higher in those patients aged 65 or more than in the younger adults for all pneumococcal disease, pneumococcal pneumonia, pneumococcal septicemia and pneumococcal meningitis ($p<0.001$). No statistically significant differences were observed for ICD-9CM code 041.2: pneumococcus infection in conditions classified elsewhere and of unspecified site.

Table 2 shows the costs of hospitalizations of pneumococcal disease by ICD-9CM code and group of age. Hospitalization costs were significantly higher for pneumococcal septicemia and pneumococcal meningitis than for pneumococcal pneumonia or pneumococcus infection in conditions classified elsewhere and of unspecified site ($p<0.001$). Costs were higher in younger patients for all diagnosis except for meningitis. Again, no statistically significant differences were observed for ICD-9CM code 041.2. Estimated cost of these hospitalisations in 2011 was more than 57 million € for pneumococcal disease and 47 million € for pneumococcal pneumonia.

When studying pneumococcal pneumonia in any diagnostic position, 11,744 hospital discharges were recorded in 2011. Considering data estimation from the International Classification of Primary Care data maintained by the Autonomous Community of Madrid, at least one underlying condition considered as risk factor for pneumococcal disease was present in 81.8% of the cases. Case-fatality rate among adult patients hospitalized with at least one underlying condition was significantly higher than among patients without comorbidities, 8.05% (CI 95% 7.37–8.73) vs 5.78% (CI 95% 5.04–6.52); $p<0.005$. When analyzing by group of age these differences are observed in all groups. It reaches significance in patients aged 18–64 y old, with 5.37% (CI 95% 4.08–6.66) vs 2.31% (CI 95% 1.58–3.03); $p<0.005$ and did not reached the significance in those aged >=65 y 8.68% (CI 95% 7.90–9.46) vs 8.42% (CI 95% 7.25–9.59); $p = 0.105$. Table 3 shows estimated annual incidence rate of hospitalization due to pneumococcal pneumonia and ODDs ratio by risk factors in adults in Spain. All the chronic condition studied increased the risk of hospitalization in adults in Spain, especially in those aged 18–64 y old.

The probability of hospitalization in patients with pneumococcal pneumonia was 73 times higher in patients with underlying conditions than in no-risk patients. In patients up to 65 y old the most important risk factors for hospitalization where immunosuppression (OR = 69.7), chronic liver disease (OR = 56.3), Diabetes Mellitus (OR = 48.7) and chronic renal disease (OR = 32.4). In older patients the most important risk factors for hospitalization where asplenia (OR = 16.7), Chronic liver disease (OR = 15.0), chronic heart disease (OR = 12.3) and immunosuppression (OR = 10.7). The highest hospitalization rates were found in those older than 65 y of age.

With the exception of asplenia, the presence of underlying conditions in immunocompetent patients increased more the risk of hospitalization in patients under 65 y old than in older patients. The effect of immunosuppression was also greater in the younger group.

Discussion

This retrospective epidemiologic study shows the hospital morbidity due to pneumococcal disease in Spain confirming the high burden of the disease, especially among the elderly, for whom pneumococcal vaccination is recommended. Our results identified asplenia, chronic respiratory disease, chronic heart disease, chronic renal disease, chronic liver disease, Diabetes Mellitus and immunosuppression as risk groups for hospitalization among patients with pneumococcal pneumonia.

The main finding of this study is that all chronic condition studied, known to be risk factors for pneumococcal disease, increased the risk of hospitalization and of death in patients with pneumococcal disease. Interestingly, the presence of underlying conditions in immunocompetent patients increased more the risk of hospitalization in those patients aged 18–64 y old than in older patients. These results go in the direction of recommending pneumococcal vaccination not only to older adults and immunocompromised patients, but also to targeted risk groups among immunocompetent young adults. This study also illustrates the high costs that pneumococcal disease hospitalizations still pose to the national health system.

Our data are in line with those from England, where there was an increased odds ratio for hospitalization and death from

Table 1. Pneumococcal disease morbidity and mortality per group of age and ICD 9CM code. CMBD (2011).

	N/ deaths			HOSPITALISATION RATE* (per 1,000 inhabitants) CI (95%)			MORTALITY RATE* (per 1,000 inhabitants) CI (95%)			CASE FATALITY RATE* (%) CI (95%)		
Age	>=18	18–64	>=65	>=18	18–64	>=65	>=18	18–64	>=65	>=18	18–64	>=65
PD	10861 / 880	3244 / 154	7617 / 726	0.285 (0.280–0.291)	0.108 (0.104–0.111)	0.960** (0.939–0.982)	0.023 (0.022–0.025)	0.005 (0.004–0.006)	0.092** (0.085–0.098)	8.102 (7.598–8.616)	4.747 (4.015–5.479)	9.531** (8.872–10.191)
PP	9995 / 718	2819 / 101	7176 / 617	0.262 (0.257–0.268)	0.094 (0.090–0.097)	0.905** (0.884–0.926)	0.019 (0.017–0.020)	0.003 (0.003–0.004)	0.078** (0.072–0.084)	7.148 (6.677–7.690)	3.583 (2.897–4.269)	8.598** (7.949–9.247)
PM	315 / 41	188 / 17	127 / 24	0.008 (0.007–0.009)	0.006 (0.005–0.007)	0.016** (0.013–0.019)	0.001 (0.001–0.001)	0.001 (0.001–0.001)	0.003** (0.002–0.004)	13.016 (9.300–16.732)	9.043 (4.943–13.142)	18.898** (12.089–25.706)
PS	536/ 119	232 / 35	304 / 84	0.014 (0.013–0.015)	0.008 (0.007–0.009)	0.038** (0.034–0.043)	0.003 (0.003–0.004)	0.001 (0.001–0.002)	0.011** (0.008–0.013)	22.200 (18.680–25.720)	15.090 (10.480–19.690)	27.630** (22.610–32.660)
Other	15 / 2	5/ 1	10/ 1	0.000 (0.000–0.001)	0.000 (0.000–0.000)	0.001 (0.000–0.002)	0.000 (0.000–0.000)	0.000 (0.000–0.000)	0.000 (0.000–0.000)	13.333 (0.000–33.869)	20.000 (0.000–65.061)	10.000 (0.000–33.594)

Notes. PD: Pneumococcal disease, including PP, PS, PM and Other; PP: 481 pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]; PM: 320.1 pneumococcal meningitis, PS: 038.2 pneumococcal septicemia and Other: 041.2 pneumococcus infection in conditions classified elsewhere and of unspecified site

*Differences in rates statistically significant ($p<0.001$) per ICD-9CM code.

**Differences in rates statistically significant ($p<0.001$) per age group.

Differences in proportions were assessed by the Chi-square test. ANOVA was used for multiple comparisons. The post hoc Bonferroni correction was used to adjust statistical significance for multiple comparisons Poisson regression was used to assess differences in the hospitalization rate, mortality rate and case-fatality rate by age group and ICD-9CM code.

Table 2. Pneumococcal disease costs per group of age and ICD 9CM code. CMBD (2011).

	Cost (€)*n		
Group of age ICD 9-CM code	>=18	18–64	>=65
PD**	5314	6645	4747
PP**	4722	5758	4315
PM	13286	12884	13880
PS	11653	12382	11097
Other	5634	5802	5550

Notes. PD: Pneumococcal disease, including PP, PS, PM and Other; PP: 481 pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]; PM: 320.1 pneumococcal meningitis, PS: 038.2 pneumococcal septicemia and Other: 041.2 pneumococcus infection in conditions classified elsewhere and of unspecified site

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**Differences in costs statistically significant ($p<0.001$) per age group.

Differences in costs were assessed by the Chi-square test. ANOVA was used for multiple comparisons. The post hoc Bonferroni correction was used to adjust statistical significance for multiple comparisons.

invasive pneumococcal disease among patients with risk factors for pneumococcal disease [13] and with those from the US, where the rate of all-cause pneumonia, pneumococcal pneumonia and invasive pneumococcal disease substantially increased with the accumulation of concurrent at-risk conditions among persons 18–49 y.[14]

Similarly to previous studies, our study confirms a higher risk of pneumococcal disease, higher incidence of hospitalization, and higher case fatality rate in those with underlying clinical conditions for whom pneumococcal vaccination is already recommended.[13]

The effect of being in a risk group was less marked in those aged 65 y and over.

This study has some limitations. The use of a Nation-wide hospital data base means that the reliability depends on the quality of the codification process reflected in the discharge report.[15] The inference of causal relationship between disease and potential complications is generally not appropriate for this study design and should be interpreted cautiously. The CMBD database does not provide information on vaccination status. Hence it is not possible to evaluate the potential effect of pneumococcal or influenza vaccination on PD related hospitalization rates.

In the present study we assumed that a differential diagnosis of severe pneumococcal disease has been confirmed. While CMBD does not give information regarding laboratory confirmation, we consider this assumption valid because it is general practice in Spanish public hospitals to confirm *S. pneumoniae* through blood culture or bronchoscopy (bronchoalveolar wash). The accuracy of ICD-9-CM for pneumococcal pneumonia has been previously assessed showing a high sensitivity and specificity for code 481.[16] Although they suggested to exclude "lobar pneumonia, organism unspecified" from code 481, we do not think that using code 481 in its entirety influences the validity of our study because although not all lobar pneumonias are pneumococcal, 80% of them are due to infection with *S. pneumoniae*.[17]

Finally, we did not study the increased risk associated to more than one co-morbidity, which is a very common situation especially in the elderly. The odds ratios shown for individual risk conditions may therefore be elevated by the existence of associated co-morbidities.

This study has not specifically been designed to assess the potential impact of the current preventive measures for the elderly and at risk population. Previous evidence from England showed that despite having PPV23 program targeted at high-risk individuals, the incidence of disease in these groups is still greatly elevated with a disproportionately high case fatality rate, especially among children and younger adults. It is unclear whether conjugate vaccines may offer an immunological advantage in these groups.[13]

Recently, a 13-valent pneumococcal conjugate vaccine (PCV13) has shown to be effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine type invasive pneumococcal disease in adults 65 y of age or older.[18]

The Spanish Association of Preventive Medicine, Public Health and Hygiene recommends a dose of PCV13 followed at 6–12 months by a dose of PPSV23 in all adults aged ≥65 years who have not previously received pneumococcal vaccine and a dose of PCV13 at least 12 months after the PPSV23 in those who have previously received pneumococcal vaccine.[19]

In countries such as US, where there is universal vaccination of children with pneumococcal conjugate vaccines—with consequent disease reduction in the adult population via herd (indirect) effects—it is unclear whether the increased risks for

Table 3. Estimated annual incidence rate of hospitalization due to pneumococcal pneumonia and ODDs ratio by risk factors in adults in Spain.

	≥ 18 Years			18–64 Years			≥65 Years		
Group of Age	Number of cases	ODDs ratio	Incidence rate /100,000	Number of cases	ODDs ratio	Incidence rate /100,000	Number of cases	ODDs ratio	Incidence rate /100,000
NO RISK GROUP	2,132	1	8.6	1,305	1	5.8	827	1	39.9
RISK GROUP	9,612	73.2 (40.6–89.7)	1,327.1	1,824	75.45 (50.6–98.3)	433.2	7,788	66.1 (30.6–95.4)	2,567.9
ASPLENIA	51	14.3 (5.5–25.7)	247.2	24	4.6 (3.1–6.7)	173.6	27	16.7 (11.2–24.9)	396.4
CHRONIC RESPIRATORY DISEASE	1,291	4.78 (1.2–7.6)	80.5	301	5.7 (5.1–6.4)	55.2	990	1.1 (1.02–1.2)	93.5
CHRONIC HEART DISEASE	3,791	12.96 (11.7–15.7)	441.7	360	13.2 (11.8–14.7)	123.4	3,431	12.3 (11.7–12.9)	605.6
CHRONIC RENAL DISEASE	914	27.6 (8.1–40.6)	607.8	99	32.4 (6.5–39.6)	329.1	815	8.7 (8.1–9.3)	677.5
CHRONIC LIVER DISEASE	431	48.04 (14.6–65.6)	757.2	216	56.3 (49.1–64.6)	541.2	215	15 (13.1–17.2)	1,263.9
DIABETES MELLITUS	2,315	39.4 (4.5–55.6)	1,104.8	377	48.7 (43.7–54.8)	449.8	1,938	2.4 (2.3–2.6)	1,541.5
IMMUSUPRESSION	774	55.76 (10.4–76.6)	736.2	402	69.7 (62.8–77.4)	637.3	372	10.7 (9.6–11.9)	884.7

Note. *Data estimated from the International Classification of Primary Care data maintained by the Autonomous Community of Madrid.

pneumococcal infections associated with certain chronic medical conditions have persisted.[20,21] Meanwhile some studies show that the indirect protection from conjugate generalized vaccination of children may benefit high-risk groups once herd immunity takes effect,[13] other studies show that despite widespread use of pneumococcal conjugate vaccines, rates of pneumonia and invasive pneumococcal disease remain disproportionately high in adults with at-risk conditions, including those with conditions not currently included in the Advisory Committee on Immunization Practices guidelines for prevention and those with multiple at-risk conditions.[14]

Although the herd effects of the infant vaccination program using the 13 valent pneumococcal conjugate vaccine (PCV13) will in time indirectly protect people at high risk, suggesting then that PCV vaccination of high-risk groups may not provide substantial additional benefit, the burden of preventable pneumococcal disease will remain high during the first years after the introduction of the infant vaccination program. Vaccinating all groups at high risk of invasive pneumococcal disease with the 13 valent pneumococcal conjugate vaccine would have a large impact on budgets, therefore targeting specific high risk groups may be more attractive although this would require general practitioners to identify subgroups among those at increased risk.[22] Our results identified that, not only older adults and immunocompromised patients, but also immunocompetent patients with underlying conditions could benefit from vaccination.

Material and methods

This retrospective study used the national surveillance system for hospital data (Conjunto Mínimo Básico de Datos; CMBD) maintained by the Ministry of Health. This system covers an estimated 98% of public hospitals. Compulsory health insurance covers an estimated 99.5% of the Spanish population, but even persons not covered by health insurance can be treated in hospitals of the Health Care System.[23,24]

All hospital discharges for pneumococcal disease and pneumococcal pneumonia among adults over 18 y of age reported in first diagnostic position in 2011 (January 1, 2011 through December 31, 2011) were obtained. The Spanish version of the 9th International Classification of Diseases (Modificación Clínica Clasificación Internacional de Enfermedades) ICD-9-CM (CIE-9-MC) codes for pneumococcal disease, (481 pneumococcal pneumonia [Streptococcus pneumoniae pneumonia], 320.1 pneumococcal meningitis, 038.2 pneumococcal septicemia and 041.2 pneumococcus infection in conditions classified elsewhere and of unspecified site) were selected.

Specific data were gathered on risk factors: asplenia, chronic respiratory disease, chronic heart disease, chronic renal disease, Diabetes Mellitus and immunosuppression.

Prevalence of underlying conditions, considered as risk factors for pneumococcal disease was estimated from the International Classification of Primary Care maintained by the Autonomous Region of Madrid. For this purpose all hospital discharges for pneumococcal pneumonia among adults over 18 y of age reported in any diagnostic position in 2011 (January 1, 2011 through December 31, 2011) were obtained. Estimated incidence rates of hospitalization due to pneumococcal pneumonia and ORs by risk factor were calculated among those exposed to a given risk factor.

Statistical methods

The incidence of hospital admissions in 2011 (per 1,000 population), rate of death (per 1,000 population) and case-fatality rate (%) were calculated. As denominator, we used data on the population covered by hospitals included in the CMBD adjusted for population figures obtained from municipal registers. It was assumed that the distribution by age of the population covered by these public hospitals was equal to the general population. Differences in proportions were assessed by the Chi-square test, and confidence intervals (95% CI) were calculated. ANOVA was used for multiple comparisons. The post hoc Bonferroni correction was used to adjust statistical significance for multiple comparisons. Poisson regression was used to assess differences in the hospitalization, mortality and case-fatality rates.

In all test the significance level used was $p < 0.05$. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS/PASW for windows, version 19.0; Chicago, IL, USA) and STATA 11 (StataCorp LP Texas, USA)

The cost to the health care system of these hospitalisations was calculated by considering the diagnostic cost group, the total cost and the number of discharges. Diagnostic cost group was based on the Diagnosis Related Groups (DRG) for hospitalized patient depending on discharge ICD classification, age, sex, and resources consumption. Each group has similar weight in hospital costs and can be applied to each related patient. DRGs calculations are made by 3M with Core Grouping System Software.[25]

Disclosure of potential conflicts of interest

This study is sponsored by Pfizer Spain. No other conflicts of interest were disclosed.

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