

Hospital incidence, in-hospital mortality and medical costs of pneumococcal disease in Spain (2008-2017): a retrospective multicentre study

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Abstract

Objective: The aim of this study was to analyse the characteristics of the patients attended with a pneumococcal disease in Spanish hospitals, to evaluate trends in hospital incidence and in-hospital mortality and to quantify patients' use of resources and medical costs.

Methods: Medical admission records of patients admitted due to pneumococcal disease between 1 Jan 2008 and 31 Dec 2017 were obtained from a Spanish hospital discharge database. Records were identified with the International Statistical Classification of Diseases and Related Health Problems, 9th and 10th version codes corresponding to pneumococcal pneumonia, bacteraemia, pyogenic arthritis, endocarditis, meningitis, peritonitis and unspecified pneumococcal infections.

Results: Admissions of 168,074 patients were analysed, with a mean age of 63.5 years (median=72; interquartile range=28). Pneumococcal pneumonia was responsible for 64.1% of all admissions, with a hospital incidence of 31.1 per 10,000 patients that decreased significantly over the study period ($p=0.002$). Hospital incidence of meningitis also displayed a decreasing trend over the study period ($p=0.003$), whereas incidence of bacteraemia and pyogenic arthritis increased significantly ($p=0.001$; $p=0.004$). Mean Charlson Comorbidity Index was 3.3 (standard deviation=2.2). In-hospital mortality was 7.0% over the study period, being the highest in patients admitted with endocarditis (17.2%). Sepsis, acute renal failure, disorders of fluid electrolyte and acid-base balance, heart failure and acute respiratory failure were strongly associated with in-hospital mortality. Mean length of hospital stay was of 11.1 days (median=22; interquartile range=26) and there was a majority of urgent admissions (95.0%); the most extended stays were registered in patients with endocarditis, meningitis and pyogenic arthritis. The mean hospital admission cost was €5676, €104.2 million annually for all

registered patients; 50.3% of all costs were associated with pneumonia, whereas the highest admission costs were registered in patients with endocarditis (€15,991) and meningitis (€11,934). Mean admission costs increased significantly over the study period for pneumonia and bacteraemia, and decreased for endocarditis.

Conclusions: The incidence of pneumococcal pneumonia and meningitis decreased over the study period after the introduction of vaccination in Spain. The advanced age of patients and presence of chronic comorbid conditions that are associated to in-hospital mortality must be taken into account when improving care protocols and upcoming vaccination plans.

Keywords: pneumococcal disease; pneumococcal pneumonia; mortality; direct medical cost.

Short title: In-hospital mortality and medical costs of pneumococcal disease in Spain (2008-2017)

Word count: 5027

Introduction

Pneumococcal disease causes a variety of clinical syndromes that range from pneumococcal pneumonia, the most common clinical presentation in adults, bacteraemia and meningitis, to less common presentations as pneumococcal endocarditis or peritonitis [1-3]. *Streptococcus pneumoniae* is one of the principal causes of severe disease worldwide, responsible for significant morbidity and mortality [4].

The annual incidence of invasive pneumococcal disease (IPD) was around the 6.2 cases per 100,000 persons in Europe in 2017, while worldwide incidence could be higher [5, 6]. Moreover, pneumococcal pneumonia alone was responsible for around 1.5 million deaths worldwide in 2015 [7]. In Spain, the hospital mortality rate of pneumococcal pneumonia was 11.6%, 1.3 per 10,000 persons between 2003 and 2007 [8].

Analyses from Soneji et al. indicated that a great number of these deaths, especially those in patients over 65 years of age, could be prevented with the generalisation of vaccination [9]. The pneumococcal polysaccharide vaccine (PPsV23) was funded by the Spanish public healthcare system around the year 2000, and the first pneumococcal conjugate vaccine (PCV13) was introduced after 2010 and funded for high risk individuals in 2012 [10]. PCV13 evidenced effectivity in preventing pneumococcal disease in vaccinated and non-vaccinated children and adults, however, certain serotypes remain active and rising [11-14]. These factors, together with the lack of a generalised public vaccination plan determine the importance of pneumococcal disease, which remains a challenge in the country and worldwide. The analysis of real-world evidence provides a clear image of current practice, which can be evaluated in the

process to approve new pharmacological interventions and to develop adequate resource allocation strategies [15, 16].

This study aimed to analyse the characteristics of the patients with a pneumococcal disease attended in Spanish hospitals, to measure in-hospital mortality and to evaluate patients' use of resources and medical costs.

Methods

Study setting

Inpatient and outpatient admission files were obtained from a Spanish National hospital discharge database that includes records from public and private hospitals, covering 90% of hospitals in Spain across Spanish regions [17]. Data is codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) after the year 2016. Centres are responsible for data codification, evaluation and confidentiality. The database is validated internally by the Unit of Health Care Information and Statistics and subjected to periodic audits; in this process, errors and unreliable data are eliminated. Only admissions in which a pneumococcal disease was listed as the admission motive in hospitals and other specialised healthcare centres in Spain between 1 Jan 2008 and 31 Dec 2017 were included in the study.

Data extraction

Records of admissions in which a pneumococcal disease was registered were identified from the specialised care database using seven ICD-9 codes (481, 790.7, 320.1, 421, 711, 567.1, 041.2) and seven ICD-10 codes (J13, R78.81, G00.1, I33.0, M00.1, K65.9, B95.3) [18,19]. Principal diagnosis was used to identify the disease and up to 20 secondary diagnoses were analysed to ensure the selection of admissions associated to pneumococcal diseases. All parameters identifying healthcare centres or medical history

were re-coded within healthcare centres to maintain records anonymised, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [20].

Study variables

The coded variables included in the analysis were: patients' sex and age, date of admission, type of admission (scheduled or urgent), date of discharge, type of discharge (including death), readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), admission motive, up to 20 secondary diagnoses registered during the admission and admission costs.

Data analysis

The first admission registered per patient in the study period was used for the analysis of patients' characteristics. All admission files were used to analyse data on the nature of admission, length of stay, readmission rate and admission costs. The analysis considered the distinct disease codes and two age groups: patients' under 65 years of age and those aged 65 years and over; data from patients under 5 years of age and in the first year of life was also evaluated. In addition, initial admissions and readmissions were compared, as well as the characteristics of deceased patients vs. non deceased. Hospital incidence was measured as the number of patients admitted with pneumococcal infections over the study period within the total number of patients included in the hospital discharge database. In-hospital mortality was calculated as the annual number of deaths registered within all patients registered with a pneumococcal disease.

Direct medical costs were calculated based on the admission costs registered in the database; these are automatically assigned according to the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health (these include all expenses incurred during the hospital admission or visit: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources). Any costs incurred outside of the hospital centre, including the costs of prescribed medication, were not available. Mean admission cost and total hospital care cost were calculated from these figures.

Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean and standard deviation (SD) or median and interquartile range (IQR) were calculated for quantitative variables. The Charlson Comorbidity Index was calculated to assess patient comorbidity status [21, 22]. The Spearman's rank correlation coefficient was calculated to assess temporal trends in hospital incidence, in-hospital mortality, length of hospital stay and costs. Two-tailed non-parametric independent t-test (Mann-Whitney *U* test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate and two-sample Z tests were used to test for differences in sample proportions, with a $p < 0.05$ considered statistically significant. The group corresponding to pneumococcal peritonitis was excluded from trend analysis due to the small number of annual cases.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP, 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

Patient characteristics

The ICD-9 and ICD-10 codes corresponding to pneumococcal infections claimed 183,758 admission files of 168,074 individual patients, which represented 0.5% of all data in the hospital discharge database. Of these, 64.1% of patients were registered with pneumonia, 21.3% with bacteraemia, 6.3% with pyogenic arthritis, 5.9% with bacterial endocarditis, 2.0% with meningitis, 0.4% with peritonitis and 0.1% of patients were registered with an unspecified infection (Table 1). Overall, mean patient age was 63.5 years (median=72; IQR=28), increasing over the study period for all conditions ($p<0.001$) (Figure 1a). A first peak appeared in age distribution between 0 and 5 years of age, to increase gradually after the 30 years of age (Figure 1b).

Mean Charlson Comorbidity Index (CCI) was 3.3 (SD=2.2), and 64.9% of the patients presented a CCI of 3 or superior. Most secondary conditions registered on admission corresponded to chronic conditions, namely essential hypertension, diabetes mellitus and hyperlipidaemia, among other conditions. The frequency of most conditions was increased with patients' age, in readmissions and in patients deceased during the admission, and CCI were significantly higher in such groups ($p<0.001$) (Table 2).

Hospital incidence and in-hospital mortality

The hospital incidence of pneumococcal diseases over the study period was 31.1 per 10,000 patients (95%CI, 22.1 to 40.1) for pneumococcal pneumonia, 10.3 per 10,000 (95%CI, 9.1 to 11.6) for bacteraemia, 4.5 per 10,000 (95%CI, 4.3 to 4.7) for pyogenic arthritis, 3.2 per 10,000 (95%CI, 3.0 to 3.3) for endocarditis, 0.96 per 10,000 (95%CI, 0.9 to 1.1) for meningitis and 1.7 per 100,000 patients (95%CI, -0.7 to 4.1) for peritonitis. The hospital incidence of pneumococcal pneumonia and meningitis displayed a decreasing trend over the study period ($p=0.002$ and $p=0.003$, respectively); whereas the hospital incidence of bacteraemia and pyogenic arthritis increased significantly ($p=0.001$ and $p=0.004$, respectively) (Figure 2a). No significant trends

were identified in the incidence of bacterial endocarditis ($p=0.865$), while data for peritonitis could not be evaluated.

Total in-hospital mortality rate was 7.0% over the study period. In-hospital mortality was 6.6% in patients with pneumonia, 3.6% in patients with bacteraemia, 2.3% in those with pyogenic arthritis, 17.2% in those with endocarditis, 11.6% in those with meningitis and 1.0% in patients with peritonitis (Table 3); in addition, it was significantly higher in patients aged 65 years and older versus those under 65 years (9.4% vs. 2.9%; $p<0.001$). The in-hospital mortality rate of pneumococcal pneumonia decreased significantly over the study period ($p=0.031$), whereas no trends were identified for the remaining conditions (Figure 2b).

Use of resources and costs

Only 0.4% of the reviewed files corresponded to outpatient visits. Mean length of hospital stay (LOHS) was 11.1 days (median=22; IQR=26), with the most extended stays registered in patients with acute and subacute bacterial endocarditis, pneumococcal meningitis and pyogenic arthritis (Table 3). LOHS decreased over time in admissions due to pneumococcal pneumonia ($p<0.001$), bacteraemia ($p=0.003$), endocarditis ($p<0.001$); no trends were found in LOHS for pyogenic arthritis or meningitis (Figure 3a). Most admissions (95.0%) were urgent or non-scheduled and the readmission rate was 11.8%. Readmission rate was also increased in patients over 65 years of age (13.1% vs. 9.6% in patients under 65 years; $p<0.001$). Readmission rate was stable over time for all conditions, and mean age of patients readmitted in the 30-days following discharge was 67.9 years (median=74; IQR=21).

The mean hospital admission cost over the study period was €5676. Admission cost was significantly higher in patients admitted with pneumococcal meningitis and acute and subacute bacterial endocarditis ($p<0.001$ vs. all conditions) (Table 4). Over the study

period, 50.3% of all costs were associated with pneumonia, bacteraemia accounted for 20% of the costs, bacterial endocarditis for 17.3%, pyogenic arthritis for 7.5%, meningitis for 4.2% and peritonitis for 0.5%.

The mean cost of scheduled admissions was significantly higher to that of urgent admissions (€8661 vs. €5521; $p<0.001$), and for readmissions vs. initial admissions (€5802 vs. €5532; $p<0.001$). Interestingly, mean admission costs were higher in patients under 65 years of age versus those aged 65 years and older ($p<0.001$) due to the high costs registered in infants with bacterial endocarditis during the first year of life (€12,554). Mean admission costs for pneumococcal pneumonia and bacteraemia increased significantly over the study period ($p=0.011$ and $p=0.023$, respectively), and decreased for endocarditis ($p=0.006$) (Figure 3b). In addition, the mean annual hospital cost of all pneumococcal infections was €104.2 million, €99.5 in 2017, considering the admissions registered in this database; 50.3% of total costs were associated with pneumococcal pneumonia, 20.2% with bacteraemia, 17.4% with endocarditis, 7.5% with arthritis, 4.2% with meningitis and 0.5% with peritonitis (Figure 3c).

Discussion

Pneumococcal disease continues to represent great morbidity and mortality worldwide through a great variety of disease presentations. The European Centre for Disease Prevention and Control (ECDC) has measured an increase on the incidence of IPD from 4.8 per 100,000 persons in 2014 to 6.2 per 100,000 persons in 2017 [5,23]. This increasing incidence highlights the challenge that pneumococcal disease represents at a global scale.

This study evaluated the hospital incidence and admission costs associated to pneumococcal disease in Spain between 2008 and 2017. Pneumococcal pneumonia was the most common clinical presentation, responsible for 64.1% of all registered hospital

admissions, followed by 21.3% of admissions associated to bacteraemia. Hospital incidence measured in this study was 31.1 per 10,000 patients for pneumococcal pneumonia, 10.3 per 10,000 for bacteraemia, 4.5 per 10,000 for pyogenic arthritis, 3.2 per 10,000 for endocarditis, 0.96 per 10,000 for meningitis and 1.7 per 100,000 patients for peritonitis. The decreasing trend found in the hospital incidence of pneumonia and meningitis over the study period could be attributable to the introduction of the PPVs23 and the PCV13 vaccines in Spain. However, the lack of a national public vaccination plan could have hampered the effects expected to derive from generalised vaccination. On the other hand, the incidence of bacteraemia and pyogenic arthritis increased over the same time period.

Mean patient age in this study was 63.5 years (median=72; IQR=28), and age was associated with an increased presence of comorbid conditions and an increased mortality. The ECDC data showed a higher incidence of IPD in patients aged 65 years and over versus that in patients under 65 years of age, reaching the 18.9 cases per 100,000 persons in 2017 [5]. A significant number of cases was also detected in newborns up to one year of age, with 14.5 cases per 100,000 persons. [5]. Hospital records analysed in this study show a similar pattern: most of the admissions were registered in patients aged 65 and over, followed by children under 5 years of age. Herein, the youngest patients were found among those with pneumococcal peritonitis.

Upon admission, a number of comorbid conditions were registered. Overall, 64.9% of the patients presented a CCI of 3 or superior, and not surprisingly, an increased CCI was associated with in-hospital death. Chronic conditions were more common in patients over 65 years of age, although this patient group also presented with a higher frequency of acute conditions, principally cardiac and renal disorders. Equally, sepsis, acute renal failure, disorders of fluid electrolyte and acid-base balance, heart failure and acute

respiratory failure were associated with mortality within the hospital setting. Cardiac and renal disease have been previously associated with in-hospital mortality in patients with pneumococcal pneumonia, and their role in overall mortality is not surprising [24]. Overall mortality was 7.0% over the study period, increasing significantly with patients' age. These figures correlate with previous evaluations; the CDC estimated a case-fatality rate for pneumococcal pneumonia of the 5%–7% [4]. Herein, the highest mortality rate was found in patients with endocarditis (17.2%) and those with meningitis (11.6%), while mortality in patients with pneumonia was 6.6%. The in-hospital mortality of pneumococcal pneumonia in Spain was reduced versus previous evaluations in the country between 2003 and 2007 (11.6%) [8].

Throughout the study period, age was a relevant component in determining patients' condition and in-hospital mortality. Similarly, the use of hospital resources was distinctive between patients in the two evaluated age groups. Patients aged 65 and over required longer hospitalisation times and were readmitted more frequently. However, overall costs per patient were higher in patients under 65 years of age due to the high costs of pneumococcal endocarditis in children. The mean direct medical cost of hospital care was €5676 per admission over the study period. In the analysis per condition, the highest admission costs were associated to pneumococcal meningitis and acute and subacute bacterial endocarditis.

Mean admission costs increased significantly over the study period for admissions related to pneumonia and bacteraemia, which should be taken into account when evaluating the growing burden that pneumococcal disease may represent for healthcare systems. At the European level, data from 2003 indicated that total the annual direct medical cost of pneumococcal disease could reach the €6 billion [25]. Direct medical costs in this study were consistent with previous findings. Hospitalisation costs in South

Korea were approximately €6900 (\$7,452) in 2011, with no clear correlation with patients' age [26]. A posterior study in the United States estimated pneumococcal infections to be responsible for direct medical costs of up to €3203 billion (\$3481 billion) in direct medical costs [27]. The total hospital cost of pneumococcal infections registered in this database in 2017 was €99.5 million. Total hospital spent in Spain was €46,028 million [28], however, the portion of these costs that derive from pneumococcal infections cannot be inferred from data in this database.

The results of this study were subjected to a series of limitations. Data included in the study was obtained from the hospital discharge database, and cannot be extrapolated to the whole Spanish population. In this terms, data obtained from electronic databases is subjected to limitations concerning data reliability, despite the efforts to validate and audit the data. The analysis of incidence and secondary conditions was limited to those registered in the hospital discharge database. Equally, the assessment of direct medical costs were limited to those registered in specialised care centres. Further studies will be required to evaluate total medical costs of pneumococcal disease and to estimate the burden of the disease. Additionally, the format of admission costs as registered in the database impeded an analysis of main cost drivers. Finally, any limitation derived from the application of univariate statistical analysis should be considered when interpreting statistical data.

Conclusions

The incidence of pneumococcal pneumonia and meningitis decreased over the study period, after the introduction of conjugated vaccination in risk groups. Nonetheless, the economic burden associated to pneumococcal disease may increase in the coming years, considering the increasing incidence of conditions as bacteraemia and pyogenic arthritis. Age and presence of comorbid conditions were crucial in determining in-

hospital mortality rate and must be taken into account when improving care protocols and vaccination plans.

Transparency section

Declaration of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of financial and other interest

The authors declare that they have no competing interests.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at <https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm>

Author contributions

JD contributed to the investigation by analysing and interpreting the burden associated to pneumococcal disease in Spain and was a major contribution in the intellectual content revision. AM analysed the current situation of pneumococcal disease in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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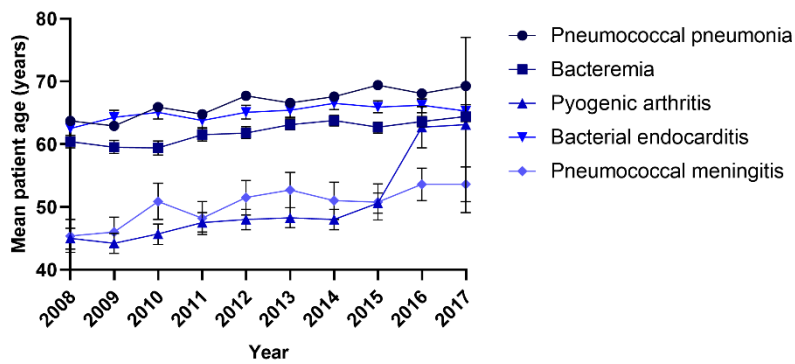
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Figures

Figure 1 (A) Mean patient age with 95% confidence interval and (B) patients age distribution by condition (2008-2017).

A.



B.

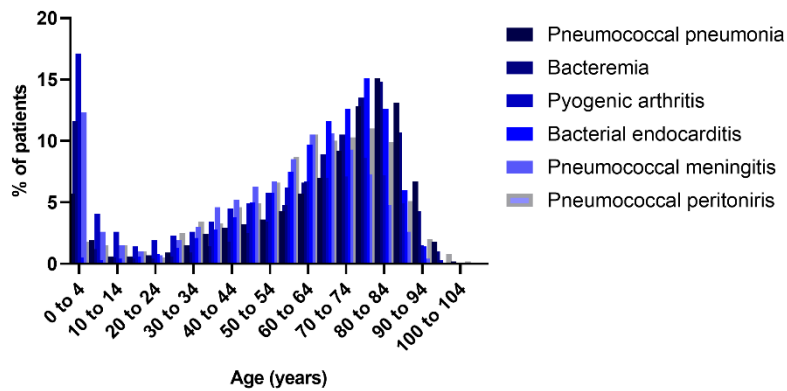
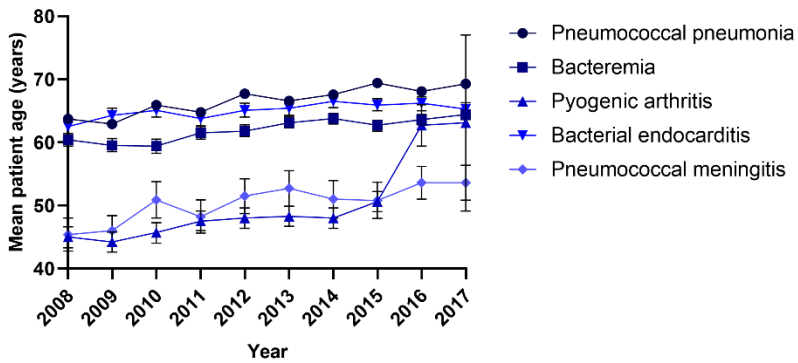


Figure 2 (A) Hospital incidence and (B) in-hospital mortality of pneumococcal disease in Spain by condition (2008-2017).

A.



B.

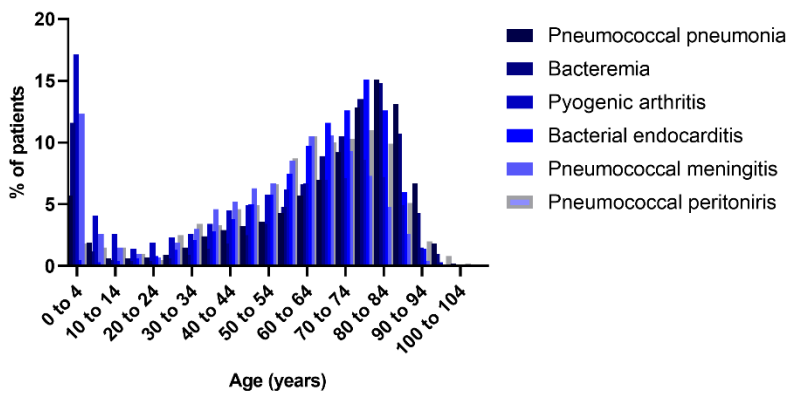
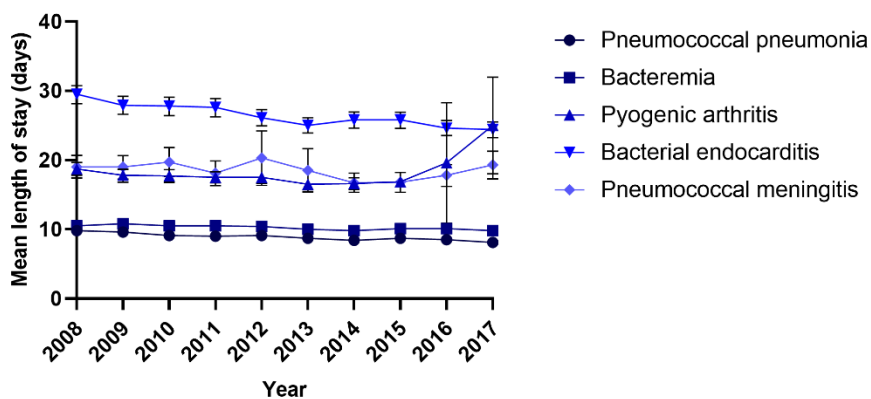
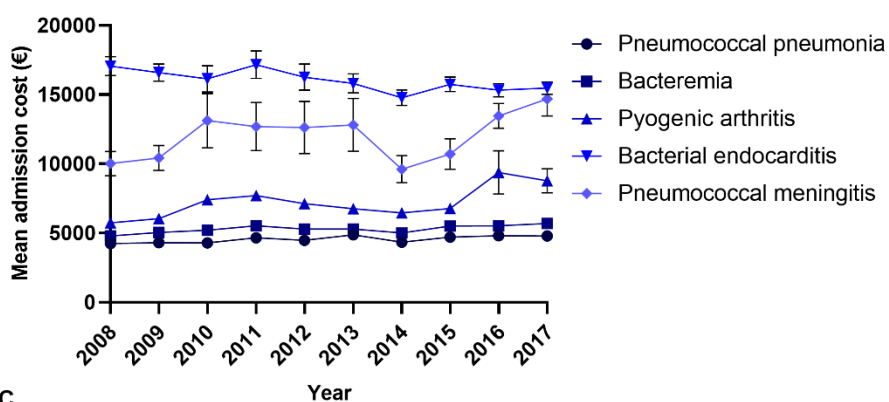


Figure 3 (A) Mean length of hospital stay with 95% confidence interval, (B) mean admission cost of pneumococcal disease per year with 95% confidence interval and (C) % of total hospital cost by condition (2008-2017).

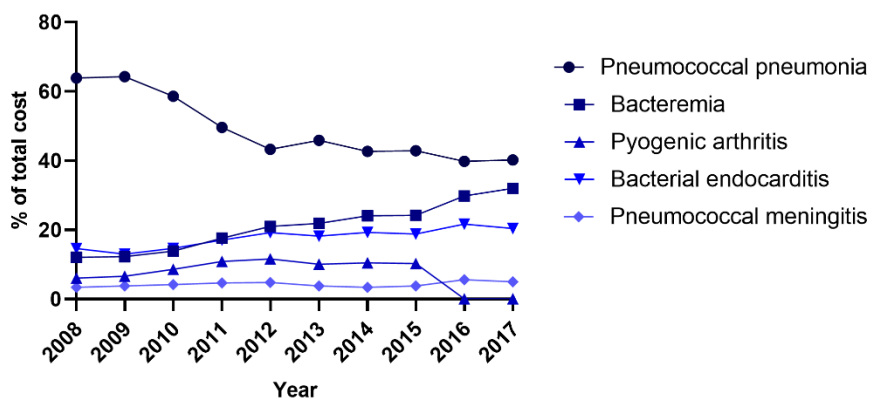
A.



B.



C.



Tables

Table 1 Number of admissions and characteristics of patients registered in the database by condition. CCI: Charlson Comorbidity Index; SD: standard deviation.

Clinical presentation	Pneumococcal pneumonia	Bacteraemia	Pyogenic arthritis	Bacterial endocarditis	Pneumococcal meningitis	Pneumococcal peritonitis
Admissions, n	116,902	39,470	11,580	11,315	3,657	683
Patients, n	107,670	35,874	10,514	9,870	3,394	609
Age, mean, median (IQR)	65.9, 75 (27)	62.3, 72 (25)	47.2, 55 (50)	65.0, 68 (22)	50.0, 57 (32)	60.7, 64 (27)
Males, %	58.4	58.3	62.9	68.2	53.3	58.9
CCI, mean (SD)	3.4 (2.2)	3.5 (2.3)	1.9 (2.0)	3.3 (2.0)	1.9 (1.8)	2.8 (2.2)
<i>Chronic conditions</i>	-	-	-	-	-	-
Unspecified essential hypertension	31.6	30.9	22.2	30.5	29.4	32.6
Diabetes mellitus	23.2	27.1	15.9	22.6	15.2	19.6
Hyperlipidaemia	16.4	17.7	11.9	18.9	16.2	21.7
Anaemia	14.4	18.1	10.9	24.2	9.3	8.7
Malignant neoplasm	12.2	30.7	5.0	8.3	5.8	28.3
Heart failure	11.7	7.7	3.4	27.0	2.8	10.9
Chronic kidney disease	10.4	15.7	6.3	14.1	2.8	8.7
Chronic ischemic heart disease	7.7	8.2	3.3	10.0	2.3	4.3
<i>Acute conditions</i>	-	-	-	-	-	-
Acute respiratory failure	27.1	3.3	1.4	7.9	8.0	2.2
Atrial fibrillation	17.7	13.1	6.2	20.0	5.1	8.7
Disorders of fluid electrolyte and acid-base balance	9.7	6.7	2.7	6.4	8.6	0.0
Acute renal failure	9.4	8.7	4.9	18.8	6.6	10.9
Sepsis	8.2	1.9	5.3	18.9	24.1	26.1

Table 2 Secondary conditions registered by age and outcome. CCI: Charlson Comorbidity Index; SD: standard deviation.

Clinical presentation	Patients < 65 years of age	Patients ≥ 65 years of age ^a	Initial admissions	Readmissions ^b	Non-deceased patients	Deceased patients ^c
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CCI, mean (SD)	1.1 (1.4)	4.6 (1.4)	3.2 (2.2)	3.9 (2.1)	3.2 (2.2)	4.5 (1.8)
<i>Chronic conditions</i>	-	-	-	-	-	-
Unspecified essential hypertension	12.7	41.4 (p<0.001)	30.6	31.0 (p=0.303)	30.6	30.9 (p=0.507)
Diabetes mellitus	11.6	30.2 (p<0.001)	22.7	27.1 (p<0.001)	23.1	25.3 (p<0.001)
Hyperlipidaemia	9.2	20.8 (p<0.001)	16.4	17.2 (p=0.004)	16.7	12.6 (p<0.001)
Anaemia	10.9	17.9 (p<0.001)	14.6	20.7 (p<0.001)	15.2	17.1 (p<0.001)
Malignant neoplasm	12.6	16.2 (p<0.001)	12.5	32.2 (p<0.001)	14.1	26.1 (p<0.001)
Chronic kidney disease	3.7	15.6 (p<0.001)	10.6	15.5 (p<0.001)	10.7	17.2 (p<0.001)
Heart failure	3.0	15.8 (p<0.001)	10.6	14.5 (p<0.001)	10.1	23.9 (p<0.001)
Chronic ischemic heart disease	2.1	10.8 (p<0.001)	7.1	10.5 (p<0.001)	7.4	8.9 (p<0.001)
<i>Acute conditions</i>	-	-	-	-	-	-
Acute respiratory failure	12.8	22.9 (p<0.001)	19.7	14.6 (p<0.001)	17.8	38.2 (p<0.001)
Atrial fibrillation	2.7	23.7 (p<0.001)	15.4	19.2 (p<0.001)	15.3	24.9 (p<0.001)
Acute renal failure	5.4	11.8 (p<0.001)	9.4	8.9 (p=0.023)	8.2	26.6 (p<0.001)
Disorders of fluid electrolyte and acid-base balance	6.1	9.8 (p<0.001)	8.5	8.0 (p=0.036)	7.6	20.5 (p<0.001)
Sepsis	8.9	7.0 (p<0.001)	7.9	6.0 (p<0.001)	5.8	35.7 (p<0.001)

^a P-value vs. patients under 65 years of age; ^b P-value vs. initial admissions; ^c P-value vs. non-deceased patients.

Table 3 Mean length of hospital stay (LOHS), percentage of urgent admissions, readmission rate and in-hospital mortality in patients with pneumococcal disease by condition.

Clinical presentation	LOHS, days, mean, median (IQR)	Urgent admissions, %	Readmission rate, %	In-hospital mortality rate (%)
Total	11.1, 22 (26)	95.0	11.8	7.0
Pneumococcal pneumonia	9.1, 7 (7)	97.2	9.0	6.6
Bacteraemia	10.2, 8 (8)	94.6	20.5	3.6
Pyogenic arthritis	17.4, 13 (15)	89.7	11.9	2.3
Acute and subacute bacterial endocarditis	26.3 (0-267)	80.5	18.1	17.2
Pneumococcal meningitis	18.6, 14 (10)	94.2	3.8	11.6
Pneumococcal peritonitis	10.7, 7 (10)	88.1	19.6	1.0
Unspecified pneumococcus infection	8.4, 7 (5)	96.7	7.9	0.7
< 65 years of age	10.8, 7 (9)	94.2	9.6	2.9
≥ 65 years of age	11.3, 8 (8)	95.6	13.1	9.4

Table 4 Mean annual direct medical costs by condition.

Clinical presentation	Pneumococcal pneumonia	Bacteraemia	Pyogenic arthritis	Bacterial endocarditis	Pneumococcal meningitis	Pneumococcal peritonitis
Mean admission cost	€ 4484	€ 5321	€ 6763	€ 15,991	€ 11,934	€ 7597
Mean cost of urgent admission	€ 4470	€ 5299	€ 6786	€ 15,578	€ 11,850	€ 7477
Mean cost of scheduled admission	€ 4950	€ 5736	€ 6578	€ 17,707	€ 13,327	€ 8591
Mean cost of an initial admission	€ 4445	€ 5162	€ 6741	€ 16,629	€ 11,419	€ 7228
Mean cost of a readmission	€ 4360	€ 5441	€ 6900	€ 14,031	€ 11,855	€ 5070
Mean cost of admissions < 22 days	€ 4048	€ 5152	€ 6208	€ 13,735	€ 9549	€ 6928
Mean cost of admissions ≥ 22 days	€ 12,807	€ 7494	€ 8548	€ 18,284	€ 21,163	€ 12,436
Mean admission cost, patients < 65 years	€ 4701	€ 5082	€ 6382	€ 16,803	€ 11,294	€ 6972
Mean admission cost, patients ≥ 65 years	€ 4376	€ 5454	€ 7408	€ 15,429	€ 13,096	€ 8254