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## Decrease in the incidence and in hospital mortality of community-acquired pneumonia among children in Spain (2001–2014)

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### ABSTRACT

**Objectives:** To describe trends in the incidence and outcomes of community-acquired pneumonia (CAP) hospitalizations among Spanish children from 2001 to 2014 and to assess the effect of the pneumococcal vaccination (PCV) coverage in this period.

**Methods:** This study was conducted using the Spanish National Hospital Database from 2001 to 2014 including subjects <18 years. We selected discharges with a primary diagnosis of CAP.

Study variable included age, sex, comorbid conditions, procedures, isolated pathogens and hospital outcome variables.

In order to estimate the effect of coverage of pneumococcal vaccination in hospitalizations for CAP, we used the number of commercialized doses of PCV (PCV7 PCV10, and PCV13) for each year.

Incidence rates of admissions for CAP were calculated by dividing the number of admissions per year, sex, and age group by the corresponding number of people in that population group according to the census data.

**Results:** We identified 194,419 admissions for CAP. Incidence rate was highest among children younger than 2 years and decreased significantly by 3.67% per year over the study period in this age group. Among children aged 2–4 years incidence of CAP seem to decrease after year 2009. *S. pneumoniae* isolations decreased significantly over time but virus isolations increased. In children aged <2 years and 2–4 years increase in PVC was associated to a decrease in the incidence of CAP hospitalizations.

Overall crude in hospital mortality following CAP fell significantly from 4.1‰ in 2001–2003 to 2.8‰ in 2012–2014.

**Conclusions:** CAP incidence rates decreased significantly among children <2 years of age from 2001 to 2014. *S. pneumoniae* isolations decreased significantly over time but virus isolations increased. In hospital mortality paralleling CAP fell significantly in children and adolescents from 2001 to 2014. Improvement in vaccination coverage seems to have a mitigating effect on hospitalizations and outcomes for CAP in children.

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### 1. Introduction

Community-acquired pneumonia (CAP) is a leading cause of pediatric hospitalization [1]. In the US the Etiology of Pneumonia in the Community Study (EPIC) reported that the annual incidence of pneumonia was 15.7 cases per 10,000 children, with the highest rate among children younger than 2 years of age [2].

Significant reduction in CAP after widespread uptake pneumococcal conjugate vaccine (PCV) have been previously reported

[3,4]. A population-based time-trend analysis of Hospital Episode Statistics data in England concluded that childhood bacterial pneumonia decreased by 19% following the introduction of the PCV7 pneumococcal conjugate vaccination to the national childhood immunization programme [5]. In the US, an additional 27% decline in pneumonia hospitalizations was reported among children aged <2 years by 2012, after the use of PCV13 instead of PCV7 [6].

Secular trends in incidence and outcomes of CAP among children and adolescents have been examined [2,7,8]. Lee et al reported decreases in the rate of CAP discharges of 21.9% in children younger than 1 year of age, but appear to be increasing in children >5 years [7]. Recently Griffin et al using data from the

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Nationwide Inpatient Sample database concluded that the annual rate of hospitalization for pneumonia among children younger than 2 years of age declined by 551.1 per 100,000 children [4]. In Spain (Madrid region) in children <15 years of age, the incidence of invasive pneumococcal disease was significantly reduced from 17.1 per 100,000 population in 2007–2010 to 7.7 per 100,000 population in 2011–2012 [9].

In Spain pneumococcal vaccination was started in year 2002 with PCV7 that was used until 2010. PCV10 was introduced in year 2009 and used until 2014 and PCV13 introduced in 2010 and is actually used [10].

However, to our knowledge, no previous studies have investigated national trends in the incidence, characteristics and outcomes of CAP in children and adolescents in Spain and its association with pneumococcal vaccine coverages.

In this study, we used national discharge data to examine trends in incidence and outcomes of CAP among patients younger than 18 years of age in Spain from 2001 to 2014. In particular we analyzed patient comorbidities, diagnostic and therapeutic procedures, pneumonia pathogens isolations and in-hospital outcomes such as readmission, in-hospital mortality (IHM) and length of hospital stay (LOHS). Also we estimated the effect of pneumococcal vaccination coverage in children and adolescents in hospitalizations for CAP in Spain.

## 2. Material and methods

This retrospective, observational study was conducted using the Spanish National Hospital Database (CMDB, *Conjunto Mínimo Básico de Datos*) which compiles all public and private hospital data, covering more than 98% of hospital admissions [11]. The CMDB includes patient variables (sex, date of birth), admission and discharge dates, up to 14 discharge diagnoses, and up to 20 procedures performed during the hospital stay [11].

We analyzed data collected between January 1, 2001 and December 31, 2014 for subjects younger than 18 years of age.

The criteria for diseases and procedures were defined according to the ICD-9-CM, which is used in the Spanish CMDB.

We selected discharges for patients with a primary diagnosis of CAP (codes: 480–488, 507.0–507.8).

Irrespective of the position at the diagnoses coding list, we included all those underlying medical conditions, adverse in-hospital events and risk factors that constitute an indication for pneumococcal vaccination among children in accordance with recommendation set by the Spanish MHSSE [10]. By last, we identified procedures and pathogens documented during hospitalizations for pneumonia (*Supplementary Methods*). According to the CMDB methodology only that pathogens that are lab-confirmed can be codified [12].

We estimated the proportion of readmission (patients that had been discharged from the hospital within the previous 30 days), the median of LOHS and IHM. IHM is defined by the proportion of patients who died during admission for each year of study is expressed per 1000 hospitalizations because sometimes the values obtained are very small (<1%).

In order to estimate the effect of coverage of pneumococcal vaccination in hospitalizations for CAP, we used the number of commercialized doses of PCV for each year. This data was provided to the investigators by the Spanish Medicines Agency of the Spanish MHSSE. In order to estimate the coverage for each age group, along the study period, we made three assumptions; (i) every commercialised dose was administered; (ii) every vaccinated child receive the complete four doses schedule (3 + 1); and (iii) all vaccines were administered to children under 12 months of age. Given this assumptions we only assessed the effect of vaccination among children aged 0 to 4 years.

### 2.1. Statistical analysis

To assess time trends, the incidence rates of admissions for CAP were calculated per 100,000 inhabitants, according to sex. We calculated yearly CAP-specific incidence rates by dividing the number of admissions per year, sex, and age group by the corresponding number of people in that population group according to the data from the Spanish National Institute of Statistics, as reported on December 31 of each year [13].

In our study we used log linear Joinpoint regression to identify the period in which trend changes in CAP incidence rates occurred by age groups for each year [14]. The Joinpoint Regression Program, version 4.0.4, was used for the analysis.

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for CAP. Variables are expressed as proportions or means with standard deviations (LOHS).

Time was divided in seven periods namely 2001–mid-2002 (pre vaccine introduction) mid 2002–2003, 2004–2006, 2007–2008, 2009, 2010–2011 and 2012–2014. Year 2009 was analyzed separately as this year the H1N1 influenza pandemic took place affecting the main study variable [15].

A time trend analysis was performed using Poisson regression, adjusted by age and sex when needed, for incidences,  $\chi^2$  test for linear trend (proportions), and ANOVA (means), as appropriate.

Lastly, we performed logistic regression analyses with mortality as a binary outcome using age, sex, comorbidities, readmission, diagnostic and therapeutic procedures, pathogens and year of admission as independent variables. Estimates were Odds Ratios (OR) with their 95% confidence intervals.

To conduct the multivariable regression models (logistic and Poisson) we did the following steps [16,17]: (i) Univariate analysis of each variable. (ii) Selection of variables for the multivariate analysis. We include all the variables whose univariate test was significant and those we considered scientifically relevant according to the references reviewed. (iii) Following the fit of the multivariate model the importance of each variable included in the model was verified. This included the examination of the Wald statistic for each variable and comparison of each estimated coefficient with the coefficient from the univariate model containing only that variable. Variables that do not contribute to the model based on these criteria were eliminated and a new model was fitted. The new model was compared to the old model using the LR test. Furthermore, estimated coefficients for the remaining variables were compared to those from the full model. This process of deleting, refitting and verifying continues until all the important variables are included in the model. (iv) Once the model was obtained, we looked more closely at the variables included (linearity) and checked for interactions in the model.

Statistical analyses were performed using Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at  $p < 0.05$  (2-tailed).

### 2.2. Ethical aspects

Since CMDB data have no personal identifiers, this study was considered to be exempt from review of the IRB's of the Rey Juan Carlos University.

## 3. Results

From 2001 through 2014, we identified a total of 194,419 admissions for CAP as primary diagnosis in patients aged <18 years in Spain. Boys accounted for 54.2% of total ( $n = 105,374$ ).

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