



## Different vaccination strategies in Spain and its impact on severe varicella and zoster<sup>☆</sup>



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### ABSTRACT

Varicella vaccines available in Spain were marketed in 1998 and 2003 for non-routine use. Since 2006 some regions decided to include varicella vaccination in their regional routine vaccination programmes at 15–18 months of age. Other regions chose the strategy of vaccinating susceptible adolescents.

This study shows the trends in severe varicella zoster virus infections through the analysis of the hospital discharges related to varicella and herpes zoster in the general population from 2005 to 2010 in Spain.

A total of 11,125 hospital discharges related to varicella and 27,736 related to herpes zoster were reported during the study period. The overall annual rate of hospitalization was 4.14 cases per 100,000 for varicella and 10.33 cases per 100,000 for herpes zoster. In children younger than 5 years old varicella hospitalization rate significantly decreased from 46.77 in 2005 to 26.55 per 100,000 in 2010. The hospitalization rate related to herpes zoster slightly increased from 9.71 in 2005 to 10.90 per 100,000 in 2010. This increase was mainly due to the significant increase occurring in the >84 age group, from 69.55 to 97.68 per 100,000. When gathering for regions taking into account varicella vaccine strategy, varicella related hospitalizations decreased significantly more in those regions which included the vaccine at 15–18 months of age as a routine vaccine comparing with those vaccinating at 10–14 years old. No significant differences were found in herpes zoster hospitalization rates regarding the varicella vaccination strategy among regions.

Severe varicella infections decreased after implementation of varicella vaccination in Spain. This decrease was significantly higher in regions including the vaccine at 15–18 months of age compared with those vaccinating susceptible adolescents.

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### 1. Introduction

Primary varicella is an acute, common and highly contagious disease caused by the varicella-zoster virus (VZV), which occurs in epidemics among pre-school and school-aged children and leaves lasting immunity. It is considered a mild or moderate disease with an increased risk of complications in immunocompromised individuals, adults and neonates if maternal varicella is temporally close to birth, however, even immunocompetent healthy children

can develop serious complications, including central nervous system involvement, pneumonia and secondary bacterial infections [1–4]. Herpes zoster occurs following reactivation of latent VZV infection and presents with a painful vesicular rash, which frequently in older individuals leads to prolonged pain, post-herpetic neuralgia (PHN), with a major impact on quality of life [5].

In the absence of vaccination, varicella virus spread widely infecting the majority of the population during childhood. In 1995 the first vaccine against varicella was introduced in the children vaccination calendar of the USA and a reduction in the number of varicella cases and the hospitalizations related to its complications was observed in the subsequent years [6].

In Spain, vaccination policies are the responsibility of the 19 regional governments. Two varicella vaccines are available in Spain: Varilrix<sup>®</sup> since 1998 for hospital indication and risk groups, e.g. immunocompromised patients, their household contacts and postpartum and nursing mothers without evidence of immunity,

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and Varivax® for active immunization in the primary prevention of varicella infection in healthy susceptible from 12 months of age since 2003. The vaccines were neither financed nor reimbursed by the public health care system, but recommended by the Spanish Association of Paediatricians and prescribed by paediatricians with the parents paying the full cost of vaccination. Starting in late 2006, four regions of Spain, accounting for a 15% of the Spanish population, included varicella vaccination in their routine childhood schedule at 15–18 months of age with coverage around 90%: two autonomous regions, Madrid (13.6% of the National population) and Navarra (1.3%), and the two autonomous cities located in the African continent, Ceuta (0.17%) and Melilla (0.15%). They also vaccinate susceptible children at 10–14 years, Madrid and Ceuta with one dose and Melilla and Navarra with two doses [7,8].

The other 15 autonomous regions (85% of the Spanish population) vaccinate susceptible children at 10–14 years with one (Andalucía, Balearic Islands, Cantabria and Extremadura; 24% of the Spanish population) or two doses (Aragon, Asturias, Canary Islands, Castilla-Leon, Castilla La Mancha, Catalonia, Galicia, La Rioja, Murcia, Valencia and Basque Country; 61% of the Spanish population). In these regions, there is an important number of children being vaccinated at 15–18 months in the private market. The estimated vaccination coverage in these 15 regions was 32% in 2008–2010, ranging from 12% to 64% (distribution data provided by IMS Health).

A national vaccination schedule will be implemented in 2014 and the varicella vaccine will be included at 12 years of age with two doses.

The herpes zoster vaccine that showed a markedly reduced morbidity from herpes zoster and post-herpetic neuralgia among older adults in several countries [9] is not available in Spain.

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 hospitalizations and, in general, is not subject to the limitations of outpatient surveillance systems. This database has been used for research purposes including epidemiological studies on varicella and other infectious diseases [10–12].

This epidemiological retrospective study was designed to provide population-based estimates of the burden of hospitalization for varicella and herpes zoster during a 6 years period (2005–2010) and to assess the impact in severe varicella and herpes zoster of two different vaccination strategies that were implemented in different Spanish regions since 2006.

## 2. Methods

The national information system for hospital data (Conjunto Mínimo Básico de Datos; CMBD) includes an estimated 98% of admissions in public hospitals, covering 99.5% of the Spanish population [13–15].

All varicella or herpes zoster related hospitalizations reported in any diagnostic position from January 1st, 2005 through December 31st, 2010 were analyzed. The 9th International Classification of Diseases ICD-9-CM (CIE-9-MC) codes for varicella (052.0, 052.1, 052.2, 052.7, 052.8, 052.9), and herpes zoster (053.0, 053.1, 053.10, 053.11, 053.12, 053.13, 053.19, 053.2, 053.20, 053.21, 053.22, 053.29, 053.7, 053.71, 053.79, 053.8, 053.9) were selected. Diagnostic codes in the primary diagnostic position were used for sensitivity analyses.

### 2.1. Statistics

The annual incidences of hospital admissions both in the general population and by group of age were calculated. Poisson regression was used to assess differences in the hospitalization rate during

the study period. To evaluate the different vaccination strategies that were implemented in different Spanish regions since 2006 a difference in difference model was used [16]. For this specific aim, data already published by this group (from 1997 to 2004) [17–19] were also included in the analysis in order to increase the temporal series and stabilize the model.

The following regression equation was used to estimate the difference in difference model applying the incidence rate ratio interpretation of the Poisson model.

$$y_{it} = \exp(\alpha_1 \text{TREAT}_i + \alpha_2 \text{PAST}_i + \alpha_3 \text{TREAT} * \text{PAST}_i + e_{it})$$

Here  $y_{it}$  is the average hospitalization rate in a specific region  $i$  of Spain ( $n=19$ ) for a given year  $t$ , (1997–2010);  $\alpha_1$  describes the effect of the region forming part of the group of 4 with the infant vaccination schedule (TREAT=1) vs. forming part of the 15 regions recommending vaccination between 10 and 14 years of age;  $\alpha_2$  describes the effect of the time discontinuity with post 2006 (PAST=1) and pre 2006 (PAST=0);  $\alpha_3$  is the difference in difference effect estimate of the infant vaccination schedule vs. children vaccination independent of the temporal trend and underlying region specific, but strategy independent effects.

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, TX, USA)

## 3. Results

A total of 11,125 hospital discharges related to varicella were reported during the 6-year study period, corresponding to an annual incidence of hospitalization of 4.14 per 100,000, that decreased significantly ( $p=0.036$ ) from 4.53 per 100,000 in 2005 to 2.95 per 100,000 in 2010 (Table 1). Varicella was coded as principal diagnose in 67% of the hospitalizations. When restricting to only principal diagnose, the hospitalization rate decreased ( $p=0.041$ ) from 3.06 (CI 95%: 2.90–3.23) per 100,000 in 2005 to 1.92 (CI 95%: 1.79–2.04) per 100,000 in 2010. The median age of the patients was 4 (IQR: 1–32) years old, both when only principal diagnose or any diagnostic position where considered.

More than 50% of the hospitalizations occurred in children <5 years old. The hospitalization rate in this group of age significantly decreased ( $p=0.020$ ) from 46.77 (CI 95%: 43.81–49.73) per 100,000 to 26.55 (CI 95%: 24.50–28.60) per 100,000 during the study period (Fig. 1).

Regarding herpes zoster, a total of 27,736 hospital discharges were reported during the 6-year study period, corresponding to an annual incidence of hospitalization of 10.33 per 100,000. This rate did not increase significantly ( $p=0.794$ ) (Table 1). Herpes zoster was coded as principal diagnose in 23% of the hospitalizations. When restricting to only principal diagnose, the hospitalization rate was stable (2.38 (CI 95%: 2.24–2.53) per 100,000 in 2005 to 2.35 (CI 95%: 2.21–2.49) per 100,000 in 2010;  $p=0.990$ ). The median age of the patients was 67 (IQR: 49–78) and 74 (IQR: 61–82) years old when only principal diagnose and any diagnostic position where considered, respectively.

More than 50% of the hospitalizations occurred in adults older than 75 years old (17% in older than 85%). The hospitalization rate in older groups of age increased during the study period, reaching statistical significance ( $p=0.026$ ) in older than 84 years old, from 53.73 (CI 95%: 51.94–55.52) per 100,000 in the period 1997–2005 to 97.68 (CI 95%: 91.62–103.73) per 100,000 in 2010 (Fig. 2).

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