ORIGINAL RESEARCH

Hospitalization Burden Related to Herpes Zoster Infection in Spain (2016–2019)

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ABSTRACT

Introduction: Herpes zoster (HZ) and its complications still represent a significant burden for patients and health care systems. In Spain, vaccination is progressively being introduced and recommended for patients between 65 and 80 years old and patients > 18 years of age suffering from certain immunosuppression conditions. The aim of this study is to estimate the number of hospital admissions related to HZ from 2016 to 2019 in Spain.

Methods: Data were collected from the Minimum Basic DataSet (MBDS) and codified according to the Spanish version of the 10th International Classification of Disease (ICD-10-CM codes B02—B02.9). Among others, variables such as sex, age and presence of complications were included.

Results: A total of 27,642 hospitalizations were identified (90% in patients > 50 and 45.8% in patients > 80). Women represented 51.2% of the patients, and 59.9% of patients presented complications related to HZ. The hospitalization rate was 17.74, the mortality rate was 1.2, and the case fatality rate was 6.75%. All rates were significantly higher with age, among men and in complicated HZ. Immunosuppression status for which vaccination had been recommended represented 22.7% of the total cases, affecting mostly individuals > 65 and causing more deaths in those > 80 years. The estimated annual cost of hospitalization for herpes zoster was €35,738,285, and the mean cost per patient was €5172.

Conclusion: The hospitalization burden for HZ is still important in Spain. Data on the current epidemiology are important to evaluate future vaccination strategies.

Keywords: Herpes zoster; Hospitalizations; Vaccination; Epidemiology; Spain

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Key Summary Points

Hospitalization burden due to herpes zoster (resulting after reactivation on varicella zoster virus from its latent state) can have a great impact on healthcare systems

Sex, age, immunosuppression, and other underlying chronic conditions are risk factors for hospitalization due to herpes zoster-associated complications

We observed an increasing trend in Spain, which demonstrates that the hospitalization rate related to herpes zoster has doubled over the last 20 years

In Spain, vaccination is recommended for the elderly and for immunosuppressed patients, regardless their age

Despite the low rate of mortality, a good understanding of the epidemiology of hospitalizations due to herpes zoster can tackle the burden on healthcare and evaluate future prevention strategies

INTRODUCTION

Herpes zoster (HZ) results from reactivation of varicella zoster virus (VZV), which stays latent in the sensory ganglia of individuals previously infected during childhood,e.g., with chickenpox. HZ causes rash and severe pain followed by a vesicular eruption in the corresponding dermatome [1]. In 20–50% of the cases, it leads to complications, especially post-herpetic neuralgia (PHN), defined as persisting pain 1 month from the beginning of the skin lesions. Other complications may include otic, ocular and central nervous system (CNS) involvement [1].

Several risk factors have been identified, including female sex and age, with 68.8% of the cases and 80.2% of the hospitalizations registered in individuals aged ≥ 50 and 97.2% of the deaths of individuals > 65 [2]. Other risk factors

for hospitalization may include immunosuppression, certain chronic conditions, genetics, depression, psychologic stress and mechanical trauma [3].

Currently, treatments for HZ and PHN are mainly symptomatic, with limited efficacy [4]. In terms of prevention of HZ, two vaccines were approved by the European Medicines Agency (EMA): Zostavax ® (ZVL), a single-dose live attenuated vaccine, and Shingrix ® (RZV), a two-dose recombinant vaccine [5]. In 2018, the Advisory Committee on Immunization Practices (ACIP) recommended the use of Shingrix over Zostavax, as it may be administered to immunocompetent adults aged > 50 years, adults with chronic medical conditions and immunocompromised individuals in certain situations [6]. In Spain, the Ministry of Health intends to progressively incorporate vaccination with Shingrix and has recently recommended its prioritization among: (1) the general population aged 65–80 years, starting with the 80-year-old cohort, and (2) patients aged > 18 years with hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), hematologic tumors and solid tumors undergoing chemotherapy as well as individuals infected with human immunodeficiency virus (HIV) and patients with rheumatoid arthritis (RA) receiving anti-JAK therapy [7].

In Europe, the annual incidence of HZ is 2–4.6 cases per 1000 population. In Spain, 3–5 cases per 1000 were estimated from 1998 to 2018, with an annual average number of hospitalizations of 3022 per 100,000 and an average number of deaths of 19 per year [2]. Despite low mortality rates, HZ and PHN result in a significant burden for patients and health care systems, which is expected to increase [3]. A good understanding of the epidemiology of HZ is essential to evaluate ongoing and future prevention strategies.

We aim to estimate the burden of herpes zoster-related hospitalizations from 2016 to 2019 in Spain. Given that HZ vaccines are already available, our study may have considerable value for public health policy decision-making.

METHODS

Study Design

We performed a retrospective epidemiologic study of all hospital admissions related to HZ during the period 2016–2019 in Spain. Data were collected from the Minimum Basic Data Set (MBDS) from the Spanish Ministry of Health and codified according to the Spanish version of the 10th International Classification of Disease (ICD-10-CM). We included all hospital discharges with HZ codified in any diagnostic position (primary or secondary). For each case, information about age, sex, region of Spain, length of stay, outcome and comorbidities was collected. We classified HZ cases as uncomplicated (code B02.9) or complicated (the remaining B02 codes). Complicated HZ included encephalitis, meningitis or other nervous system complications, ophthalmic affection, disseminated HZ and other unspecified complications (please see Supplementary Table 1). For comorbidities, we selected and codified those in which vaccination has been specifically recommended by the Spanish Ministry of Health: hematopoietic stem cell transplantation, solid organ transplantation, anti-JAK therapy in patients with rheumatoid arthritis, HIV, hematologic tumors and solid tumors undergoing chemotherapy (please see Supplementary Table 2).

Statistical Analysis

The total hospitalization rate (number of admissions diagnosed with HZ per 100,000 population), median length of stay (total length of stay/total number of hospitalizations), mortality rate (number of deaths at hospital per 100,000 population) and case-fatality rate (number of deaths at hospital/number of hospitalizations, expressed in percentage) were calculated from the overall period 2016–2019 in Spain for each (autonomous) region and for all the comorbidities mentioned before. The annual hospitalization rate in Spain was also calculated per year. The total Spanish population stratified by sex and age was used as the denominator in each case; the rates were adjusted by age. Finally, the total and average costs per HZ hospitalization (total annual cost/total number of hospitalizations per year, in euros) were estimated.

All analyses were performed by sex and age for complicated and uncomplicated HZ cases (according to the ICD-10-CM codes). The following age groups were created: < 50, 50–59, 60–69, 70–79 and ≥ 80 years. For the analysis performed by comorbidities, we decided to state three groups (< 65, 65–79 and ≥ 80) based on the recommendations for vaccination made by the Spanish Ministry of Health.

The Statistical Package for Social Sciences (SPSS/PASW, version 27) was used to perform statistical analyses. For statistical comparison, a p value of 0.05 was considered significant. Poisson regression was used to compare hospitalization rates. Logistic regression was used to analyze case fatality rates. Mean hospital stay lengths were compared using ANOVA. The patient information was anonymized and de-identified prior to the analysis in compliance with ethics guidelines. The study was performed in accordance with the Helsinki Declaration 1964 and its later amendments. The Rey Juan Carlos University Ethics Committee Board ruled that no formal ethics approval was required for this study.

RESULTS

A total of 27,642 cases of HZ were registered during the period 2016–2019, of which 90% were patients > 50 years old and 45.8% were individuals > 80. Almost 52% of the cases were found in women, and 59.9% were related to complicated HZ (Table 1).
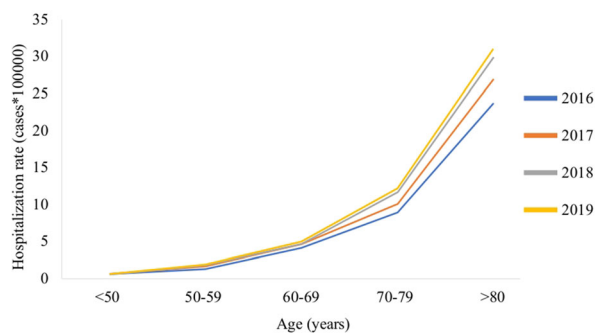
The hospitalization rate during the study period was 17.74 hospitalizations per 100,000 inhabitants (CI 95% 17.53–17.95). This rate increased significantly with age, reaching a maximum in the population ≥ 80 years (104.58 per 100,000 inhabitants). Significantly higher rates were also observed among men in both uncomplicated and complicated HZ. This can be found in all age groups except for the total group, which becomes significant when

Table 1 Hospitalization rate, mortality rate and case fatality rate due to herpes zoster: total and by age group, sex and presence of complications

Group of age (years)	Cases (N)			Hospitalization rate (cases*100,000/95% CI)			Mortality rate (cases*100,000/95% CI)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Total									
< 50	1381	1298	2679	3.31 (3.14–3.48)	3.22 (3.04–3.4)	3.27 (3.15–3.39)	0.04 (0.02–0.06)	0.03 (0.01–0.05)	0.04 (0.03–0.05)
50–59	1043	968	2011	7.74 (7.27–8.21)	7.07 (6.62–7.52)	7.4 (7.08–7.72)	0.42 (0.31–0.53)	0.22 (0.14–0.3)	0.32 (0.25–0.39)
60–69	2223	1664	3887	22.57 (21.63–23.51)	15.68 (14.93–16.43)	18.99 (18.39–19.59)	1.19 (0.97–1.41)	0.63 (0.48–0.78)	0.9 (0.77–1.03)
70–79	3549	2843	6392	52.79 (51.05–54.53)	35.05 (33.76–36.34)	43.09 (42.03–44.15)	3.32 (2.88–3.76)	1.58 (1.31–1.85)	2.37 (2.12–2.62)
≥ 80	5152	7521	12,673	121.81 (118.4–125.1)	104.58 (102.2–106.9)	110.96 (109.0–112.9)	12.11 (11.06–13.16)	9.79 (9.07–10.5)	10.65 (10.05–11.25)
Total	13,348	14,294	27,642	17.57 (17.27–17.87)	17.89 (17.6–18.18)	17.74 (17.53–17.95)	1.22 (1.14–1.3)	1.18 (1.1–1.26)	1.2 (1.15–1.25)
Uncomplicated									
< 50	597	663	1260	1.43 (1.32–1.54)	1.65 (1.52–1.78)	1.54 (1.46–1.62)	0.03 (0.01–0.05)	0.01 (0–0.02)	0.02 (0.01–0.03)
50–59	543	486	1029	4.03 (3.69–4.37)	3.55 (3.23–3.87)	3.79 (3.56–4.02)	0.31 (0.22–0.4)	0.12 (0.06–0.18)	0.22 (0.16–0.28)
60–69	929	795	1724	9.43 (8.82–10.04)	7.49 (6.97–8.01)	8.42 (8.02–8.82)	0.6 (0.45–0.75)	0.39 (0.27–0.51)	0.49 (0.39–0.59)
70–79	1341	1190	2531	19.95 (18.88–21.02)	14.67 (13.84–15.5)	17.06 (16.4–17.72)	1.34 (1.06–1.62)	0.76 (0.57–0.95)	1.02 (0.86–1.18)
≥ 80	1747	2804	4551	41.31 (39.37–43.25)	38.99 (37.55–40.43)	39.85 (38.69–41.01)	4.75 (4.09–5.41)	3.5 (3.07–3.93)	3.97 (3.6–4.34)
Total	5157	5938	11,095	6.79 (6.6–6.98)	7.43 (7.24–7.62)	7.12 (6.99–7.25)	0.53 (0.48–0.58)	0.47 (0.42–0.52)	0.5 (0.46–0.54)
Complicated									
< 50	784	635	1419	1.88 (1.75–2.01)	1.58 (1.46–1.7)	1.73 (1.64–1.82)	0.01 (0–0.02)	0.01 (0–0.02)	0.01 (0–0.02)
50–59	500	482	982	3.71 (3.38–4.04)	3.52 (3.21–3.83)	3.62 (3.39–3.85)	0.11 (0.05–0.17)	0.09 (0.04–0.14)	0.1 (0.06–0.14)
60–69	1294	869	2163	13.14 (12.42–13.86)	8.1 9(7.65–8.73)	10.57 (10.12–11.02)	0.59 (0.44–0.74)	0.24 (0.15–0.33)	0.41 (0.32–0.5)
70–79	2208	1653	3861	32.84 (31.47–34.21)	20.38 (19.4–21.36)	26.03 (25.21–26.85)	1.98 (1.64–2.32)	0.81 (0.61–1.01)	1.34 (1.15–1.53)
≥ 80	3405	4717	8122	80.51 (77.81–83.21)	65.59 (63.72–67.46)	71.11 (69.56–72.66)	7.35 (6.53–8.17)	6.28 (5.7–6.86)	6.68 (6.21–7.15)
Total	8191	8356	16,547	10.78 (10.55–11.01)	10.46 (10.24–10.68)	10.62 (10.46–10.78)	0.69 (0.63–0.75)	0.7 (0.64–0.76)	0.7 (0.66–0.74)

Group of age (years)	Case fatality rate (%/95% CI)			Median length (days/IQR)		
	Male	Female	Total	Male	Female	Total
Total						
< 50	1.23 (0.65–1.81)	0.92 (0.4–1.44)	1.08 (0.69–1.47)	7 (11–4)	6 (10–3)	6 (10–3)

Table 1 continued

Group of age (years)	Case fatality rate (%/95% CI)			Median length (days/IQR)		
	Male	Female	Total	Male	Female	Total
50–59	5.47 (4.09–6.85)	3.1 (2.01–4.19)	4.33 (3.44–5.22)	7 (15–4)	7 (14–4)	7 (14–4)
60–69	5.26 (4.33–6.19)	4.03 (3.09–4.97)	4.73 (4.06–5.4)	7 (14–4)	7 (13–4)	7 (13–4)
70–79	6.28 (5.48–7.08)	4.5 (3.74–5.26)	5.49 (4.93–6.05)	8 (14–4)	7 (13–4)	7 (13–4)
≥ 80	9.94 (9.12–10.76)	9.36 (8.7–10.02)	9.6 (9.09–10.1)	7 (13–4)	7 (12–4)	7 (13–4)
Total	6.94 (6.51–7.37)	6.58 (6.17–6.99)	6.75 (6.45–7.05)	7 (13–4)	7 (13–4)	7 (13–4)
Uncomplicated						
< 50	2.01 (0.88–3.14)	0.9 (0.18–1.62)	1.43 (0.77–2.09)	6 (11–3)	6 (10–3)	6 (10–3)
50–59	7.73 (5.48–9.98)	3.5 (1.87–5.13)	5.73 (4.31–7.15)	8 (15–4)	8 (15–4)	8 (15–4)
60–69	6.35 (4.78–7.92)	5.16 (3.62–6.7)	5.8 (4.7–6.9)	8 (15–4)	8 (14–4)	8 (15–4)
70–79	6.71 (5.37–8.05)	5.21 (3.95–6.47)	6.01 (5.08–6.94)	8 (15–4)	8 (14–4)	8 (14–4)
≥ 80	11.51 (10.01–13.01)	8.99 (7.93–10.05)	9.95 (9.08–10.82)	8 (13–4)	8 (13–4)	8 (13–4)
Total	7.83 (7.1–8.56)	6.37 (5.75–6.99)	7.05 (6.57–7.53)	8 (14–4)	7 (13–4)	8 (14–4)
Complicated						
< 50	0.64 (0.08–1.2)	0.94 (0.19–1.69)	0.78 (0.32–1.24)	7 (11–4)	6 (10–3)	6 (10–4)
50–59	3.00 (1.5–4.5)	2.7 (1.25–4.15)	2.85 (1.81–3.89)	7 (14–4)	7 (13–4)	7 (13–4)
60–69	4.48 (3.35–5.61)	2.99 (1.86–4.12)	3.88 (3.07–4.69)	7 (13–4)	7 (13–4)	7 (13–4)
70–79	6.02 (5.03–7.01)	3.99 (3.05–4.93)	5.15 (4.45–5.85)	7 (13–4)	7 (13–4)	7 (13–4)
≥ 80	9.13 (8.16–10.1)	9.58 (8.74–10.42)	9.39 (8.76–10.02)	7 (12–4)	7 (12–4)	7 (12–4)
Total	6.37 (5.84–6.9)	6.74 (6.2–7.28)	6.56 (6.18–6.94)	7 (12–4)	7 (12–4)	7 (12–4)

Fig. 1 Hospitalization rate related to HZ by age group in Spain (2016–2019)

comparing age-adjusted rates The median length of stay was 7 days (IQR 13–4), with no differences by age or sex (Table 1).

During the study period, we observed a significant increase in the hospitalization rates over time in both complicated and uncomplicated HZ (Fig. 1).

The mortality rate was 1.2 deaths per 100,000 inhabitants (CI 95% 1.15–1.25), and the case fatality rate was 6.75% (CI 95% 6.45–7.05). When compared by age and sex, both rates were significantly higher with age (reaching a maximum of 10.65 per 100,000 and a 9.6% among patients ≥ 80) and among men when analyzing age-adjusted rates (Table 1).

Complicated HZ caused more hospitalizations than uncomplicated HZ. Complicated HZ caused higher mortality and case fatality rates in women ≥ 80 and men of all ages, excluding the group of 60–69 years (Table 1).

Figure 2 shows the hospitalization rate for HZ in each autonomous region of Spain. La Rioja has the highest hospitalization rate (30.81 per 100,000 inhabitants), followed by País Vasco (26.55 per 100,000 population), Castilla y León (25.86 per 100,000) and Madrid (25.24 per 100,000). Ceuta, Melilla and the Canary Islands show the lowest hospitalization rates (5.65, 5.3 and 7.94 per 100,000 population, respectively).

Among the studied comorbidities, the most common was solid tumors. We found a total of 3078 cases (11.14% of the total hospitalizations), of which 51.2% corresponded to complicated HZ. The second most common one was
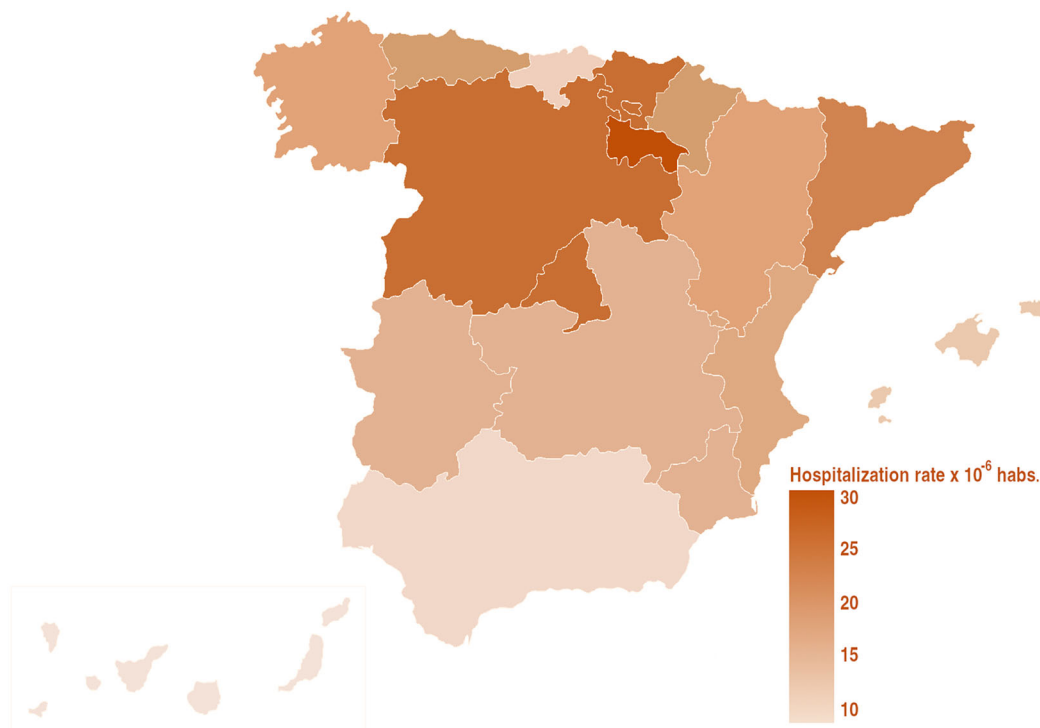
Fig. 2 Hospitalization rate related to herpes zoster in Spain

hematologic tumors, with 1237 cases identified (4.48% of the hospitalizations), of which 56.1% were related to complicated HZ. All comorbidities were more frequent in men, except for RA. Most of the cases of HSCT and HIV occurred in patients < 65. RA was more frequent in those aged > 65. Both solid and hematologic tumors were more common in the 65- to 79-year-old group. The total average length of hospital stay was 7 days, and total in-hospital mortality was 1867 cases (6.75%), of which 58% were related to complicated HZ. A significantly higher number of deaths was observed in individuals ≥ 80 years in all the groups, with no differences observed by sex (Table 2).

Hospitalizations for HZ were estimated to generate a total cost of €142.953.128 and an annual expenditure of €35,738,285 for the healthcare system. The mean cost per patient was €5172 (Table 3).

DISCUSSION

The main objective of our study was to describe and analyze the burden of hospitalizations related to HZ in Spain in a given period. We identified > 27,000 hospitalizations related to HZ infection between 2016 and 2019. We also found that the hospitalization rate was 17.74 per 100,000 population, which was slightly higher than the rates previously reported in Spain from 1998 to 2018 [8–11]. This increasing trend is consistent with the results found by the last review performed by the Ministry of Spain, which states that the hospitalization rate related to HZ has doubled within the past 20 years. In Europe, the results varied from 18.16 hospitalizations per 100,000 in Italy [12] to 24.8 hospitalizations per 100,000 population in Norway [13]. Studies conducted in the USA and Japan reported hospitalization rates of 9.92 and 17.8, respectively [14, 15]. This variation could be explained by inter-individual differences between populations, different National Health Systems, national databases and criteria for hospitalization [16, 17].

When analyzing these results, it is important to consider that several factors may have contributed to this increase. On one hand, as has been previously described, it can be attributed to an increase in the mean age of the > 85 year group related to an increase in life expectancy. As HZ incidence increases with age, a higher hospitalization rate in this group can be expected [11, 18]. Furthermore, this could also be associated with an increase in the number of hospitalizations for any cause in those aged > 75 years during the study period and with an increase in the incidence of some immunosuppressive and chronic conditions, such as diabetes, chronic obstructive pulmonary disease (COPD) and depression, which are described as risk factors for HZ [3, 10, 11]. On the other hand, as we considered hospitalizations related to HZ in any diagnostic position, we could not know whether the patient was hospitalized for HZ or developed it during the hospital stay [11], which could be a major limitation of our study.

Some differences have been observed regarding the rate of hospitalization among regions of Spain. They follow the same pattern shown in previous studies. Thus, higher rates were found in the north, whereas the Canary Islands had the lowest rates. This has been attributed to a lower seroprevalence of VZV related to geographic characteristics [9]. Additionally, a younger population is found in the Canary Islands in contrast to an older population located in northern Spain [19]. We also found an increase in hospitalizations over time in almost all regions, which is consistent with our total results [9, 19, 20].

As in similar studies, age was identified as the main risk factor for HZ, with 90% of the hospitalizations found in patients older than 50 years and 45.8% of them estimated in patients over 80 years [2, 10]. This is thought to be mainly related to the decrease in cell immunity associated with age but also to the higher incidence of comorbidities, polypharmacy and social-environmental changes associated with elderly individuals, such as institutionalization or lack of family or social support [3, 21, 22].

Although female sex is described as an independent risk factor for HZ [23], we found that both hospitalization and mortality rates were higher among men. This can be attributed to a higher incidence of associated

Table 2 Hospitalizations due to herpes zoster: clinical characteristics by sex, age group and presence of complications

Group of age (years)		Male					Female				
		< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	p^*	< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	p^*
Uncomplicated	HSCT	56 (3.64)	11 (0.59)	0 (0)	67 (1.3)	0.000	42 (2.79)	14 (0.86)	0 (0)	56 (0.94)	0.000
	SOT	64 (4.16)	61 (3.26)	5 (0.29)	130 (2.52)	0.000	55 (3.65)	39 (2.4)	7 (0.25)	101 (1.7)	0.000
	RA	9 (0.58)	38 (2.03)	33 (1.89)	80 (1.55)	0.001	34 (2.26)	72 (4.43)	67 (2.39)	173 (2.91)	0.000
	Hematologic tumours	128 (8.32)	101 (5.4)	59 (3.38)	288 (5.58)	0.000	95 (6.3)	111 (6.82)	49 (1.75)	255 (4.29)	0.000
	Solid tumors	280 (18.19)	388 (20.74)	221 (12.65)	889 (17.24)	0.000	257 (17.05)	200 (12.29)	155 (5.53)	612 (10.31)	0.000
	AIDS	160 (10.4)	14 (0.75)	1 (0.06)	175 (3.39)	0.000	116 (7.7)	1 (0.06)	0 (0)	117 (1.97)	0.000
	Lenght of stay	7 (10)	8 (11)	8 (9)	8 (10)	0.000	7 (9)	8 (10)	8 (9)	7 (9)	0.000
	Deaths	76 (4.94)	127 (6.79)	201 (11.51)	404 (7.83)	0.000	40 (2.65)	86 (5.29)	252 (8.99)	378 (6.37)	0.000
Complicated	HSCT	56 (3.15)	29 (0.96)	0 (0)	85 (1.04)	0.000	50 (3.4)	10 (0.46)	0 (0)	60 (0.72)	0.000
	SOT	64 (3.6)	114 (3.79)	7 (0.21)	185 (2.26)	0.000	52 (3.54)	53 (2.44)	3 (0.06)	108 (1.29)	0.000
	RA	15 (0.84)	51 (1.7)	55 (1.62)	121 (1.48)	0.042	42 (2.86)	89 (4.1)	104 (2.2)	235 (2.81)	0.000
	Hematologic tumours	117 (6.57)	187 (6.22)	98 (2.88)	402 (4.91)	0.000	86 (5.85)	111 (5.12)	95 (2.01)	292 (3.49)	0.000
	Solid tumors	167 (9.38)	428 (14.24)	415 (12.19)	1010 (12.33)	0.000	123 (8.37)	208 (9.59)	236 (5)	567 (6.79)	0.000
	AIDS	161 (9.04)	16 (0.53)	7 (0.21)	184 (2.25)	0.000	70 (4.76)	1 (0.05)	6 (0.13)	77 (0.92)	0.000
	Lenght of stay	7 (7.5)	8 (9)	7 (8)	7 (8)	0.000	7 (7)	7 (9)	7 (8)	7 (8)	0.000
	Deaths	41 (2.3)	170 (5.66)	311 (9.13)	522 (6.37)	0.000	30 (2.04)	81 (3.73)	452 (9.58)	563 (6.74)	0.000

Table 2 continued

Group of age (years)		Male					Female				
		< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	p^*	< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	p^*
Total	HSCT	112 (3.37)	40 (0.82)	0 (0)	152 (1.14)	0.000	92 (3.09)	24 (0.63)	0 (0)	116 (0.81)	0.000
	SOT	128 (3.86)	175 (3.59)	12 (0.23)	315 (2.36)	0.000	107 (3.59)	92 (2.42)	10 (0.13)	209 (1.46)	0.000
	RA	24 (0.72)	89 (1.82)	88 (1.71)	201 (1.51)	0.000	76 (2.55)	161 (4.24)	171 (2.27)	408 (2.85)	0.000
	Hematologic tumours	245 (7.38)	288 (5.91)	157 (3.05)	690 (5.17)	0.000	181 (6.08)	222 (5.85)	144 (1.91)	547 (3.83)	0.000
	Solid tumors	447 (13.47)	816 (16.73)	636 (12.34)	1899 (14.23)	0.000	380 (12.76)	408 (10.75)	391 (5.2)	1179 (8.25)	0.000
	AIDS	321 (9.67)	30 (0.62)	8 (0.16)	359 (2.69)	0.000	186 (6.25)	2 (0.05)	6 (0.08)	194 (1.36)	0.000
	Lenght of stay	7 (8)	8 (10)	7 (9)	7 (9)	0.000	7 (8)	7 (9)	7 (8)	7 (9)	0.000
	Deaths	117 (3.53)	297 (6.09)	512 (9.94)	926 (6.94)	0.000	70 (2.35)	167 (4.4)	704 (9.36)	941 (6.58)	0.000

Group of age (years)	Total				
	< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	p^*
Uncomplicated	98 (3.22)	25 (0.71)	0 (0)	123 (1.11)	0.000
	119 (3.91)	100 (2.86)	12 (0.26)	231 (2.08)	0.000
	43 (1.41)	110 (3.14)	100 (2.2)	253 (2.28)	0.000
	223 (7.32)	212 (6.06)	108 (2.37)	543 (4.89)	0.000
	537 (17.63)	588 (16.81)	376 (8.26)	1501 (13.53)	0.000
	276 (9.06)	15 (0.43)	1 (0.02)	292 (2.63)	0.000
	7 (9)	8 (10)	8 (9)	8 (10)	0.000
	116 (3.81)	213 (6.09)	453 (9.95)	782 (7.05)	0.000

Table 2 continued

Group of age (years)	Total				p*
	< 65 N (%)	65–79 N (%)	≥ 80 N (%)	Total N (%)	
Complicated	106 (3.26)	39 (0.75)	0 (0)	145 (0.88)	0.000
	116 (3.57)	167 (3.23)	10 (0.12)	293 (1.77)	0.000
	57 (1.75)	140 (2.71)	159 (1.96)	356 (2.15)	0.003
	203 (6.25)	298 (5.76)	193 (2.38)	694 (4.19)	0.000
	290 (8.92)	636 (12.29)	651 (8.02)	1577 (9.53)	0.000
	231 (7.11)	17 (0.33)	13 (0.16)	261 (1.58)	0.000
	7 (7)	7 (9)	7 (8)	7 (8)	0.000
	71 (2.18)	251 (4.85)	763 (9.39)	1085 (6.56)	0.000
Total	204 (3.24)	64 (0.74)	0 (0)	268 (0.97)	0.000
	235 (3.73)	267 (3.08)	22 (0.17)	524 (1.9)	0.000
	100 (1.59)	250 (2.88)	259 (2.04)	609 (2.2)	0.000
	426 (6.77)	510 (5.88)	301 (2.38)	1237 (4.48)	0.000
	827 (13.14)	1224 (14.11)	1027 (8.1)	3078 (11.14)	0.000
	507 (8.05)	32 (0.37)	14 (0.11)	553 (2)	0.000
	7 (8)	8 (9)	7 (9)	7 (9)	0.000
	187 (2.97)	464 (5.35)	1216 (9.6)	1867 (6.75)	0.000

HSCT hematopoietic stem–cell transplantation, *SOT* solid organ transplantation, *RA* rheumatoid arthritis, *AIDS* acquired immunodeficiency syndrome

*p comparison by age

Table 3 Total and average costs per HZ total hospitalization

	Average costs (€)	Total costs (2016–2019) (€)	Total annual cost (€)
Total	5172	142,953,138	35,738,285
Uncomplicated	5408	60,001,135	15,000,284
Complicated	5013	82,952,004	20,738,001

comorbidities (especially immunosuppression conditions such as HIV or tumors) and a lower average life expectancy in men [3]. When reviewing the current literature, the same discordant results were found [3, 10, 24]. Similar results were shown in the last study done in Spain by the Ministry of Health [10], while a study conducted by Esteban Vasallo et al. identified higher rates in men except for extreme ages [3], and other European studies found higher rates of hospitalization and mortality for females [24, 25].

Immunosuppression has been proven to be highly associated with HZ, as it is identified in almost one-third of patients [3, 9, 16]. When analyzing those comorbidities in which vaccination is recommended by the Ministry of Health, they represented 22.7% of total hospitalizations, 6.75% of hospital mortality and 20% of the complicated total cases. As in other studies, tumors were the most frequent comorbidity, and all comorbid illnesses were higher among men [3, 9, 26]. Although immunosuppression conditions were found in patients of all ages, most of the cases affected the 65–79-year-old group, and higher mortality rates were found in patients over 80 years for all conditions.

MBDS is a feasible and sensitive way to study the epidemiology of a disease, as it provides a large representative sample size that gives great statistical power to the study. However, it can have some limitations due to its nature. First, as we considered hospitalization related to HZ in any diagnostic position, we could not identify whether HZ was the main cause of the hospitalization. Second, as our aim was to focus on the burden of hospitalizations, we chose to analyze the number of hospitalizations and not the number of patients so several hospitalizations could occur for the same patient. Potential biases associated with the codification process should also be considered, although a positive predictive value of 89%–96% over an ICD9 diagnostic code of HZ [10] has been reported. Furthermore, ICD10 has no code for either "hematologic tumors and solid tumors undergoing chemotherapy" or "rheumatoid arthritis receiving anti JAK therapy," so we included all solid and hematologic tumors and AR cases. Finally, the MBDS does not include useful data on disease severity, microbiologic confirmation, medication and other procedures or patients' functional level and social situation. However, HZ is an easily recognizable disease that can be clearly diagnosed clinically, not resulting in an overdiagnosis or infradiagnosis.

Therefore, we consider that immunocompromised patients of all ages would benefit from vaccination with the new recombinant vaccine, especially those older than 80 years. Other common chronic conditions, such as diabetes mellitus or chronic obstructive pulmonary disease (COPD), have also been described as risk factors for HZ. Although we did not include them in our study, they have been identified as priority groups for immunization in the future [3, 5]. On the other hand, immunocompromised adults should never receive the live HZ vaccine (Zostavax) because the vaccine virus itself can cause disseminated viral infection and even death [27].

Although HZ is not in general a life-threatening disease, this condition primarily affects individuals > 80 years of age and is more prevalent among men. This population has underlying comorbitidies that may increase the risk of mortality. However, even if the mortality rate is low, HZ in a high-risk population may reduce the patient's health-related quality of life [9, 10, 19, 26].

Regarding HZ vaccination, the positive impact on epidemiologic indicators has been seen in the reduction of HZ incidence in children vaccinated against varicella [28]. Some studies propose that this impact may be greater among the elderly with high coverage

(currently between 58 and 72% of the population) [29, 30]. In Spain, it is estimated that 97% of the child population is vaccinated against varicella, but in the elderly this coverage decreases to 57%. We should be aware of preventive measures to improve later outcomes among the elderly population.

Furthermore, we have shown that our hospitalization rates are higher than those previously reported in Spain, with almost 60% of hospitalizations attributed to complicated HZ, as already reported elsewhere (48.7–53%), estimated at a cost of €35.7 million per year, which would be higher if indirect costs were also considered [3, 8]. Finally, regarding mortality, a systematic review of HZ-associated mortality in Europe reported that available data on HZ mortality are too heterogeneous to for cross-country comparisons [31].

As discussed above, the main limitation of our study is that it was based on administrative data (MBDS). Electronic health records allow for greater availability of data collection, but as long as databases such as the MBDS focus on economic management, clinical relevance may be limited. One of the aims of MBDS is to facilitate clinical research, but the validity of the dataset depends on the accuracy of clinical discharge reports. If primary or secondary diagnoses are incorrect, or incomplete, or some clinical conditions are excluded, the reliability of our dataset is not be guaranteed. We are aware that there is some discrepancy between correct and incorrect diagnoses recorded in the MBDS, and this is an important limitation of our study. Although a certain amount of misclassification errors is expected, the MBDS can provide valid information and can be a useful tool in epidemiologic studies [32, 33].

CONCLUSIONS

The burden of hospitalization related to herpes zoster is still important in Spain, as it is higher with age, among men and in immunocompromised patients. We can conclude that the main risk factors are aging and immunosuppression. The results obtained regarding the epidemiology of HZ in Spain are similar to those previously found in national and international literature. However, data on the epidemiology of HZ are needed to evaluate the potential impact of future vaccination. Finally, an interesting future research line is more detailed studies to assess its cost-effectiveness and its impact on quality of life once the HZ vaccine is introduced in a given national program.

1964 and its later amendments. The Rey Juan Carlos University Ethics Committee Board ruled that no formal ethics approval was required for this study.

Data Availability. The datasets analyzed during the current study are available from the corresponding author, Ruth Gil-Prieto, on reasonable request.

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