

# Temporal trends in herpes zoster-related hospitalizations in Italy, 2001–2013: differences between regions that have or have not implemented varicella vaccination

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## Abstract

**Background** Herpes zoster (HZ) has a relevant impact on the population in terms of incidence and complications.

**Aims** The aim of this study was to estimate the HZ-related hospitalization rates in Italy in the period 2001–2013, and to evaluate the trend of hospitalizations in the course of time pointing out any differences between regions that have or have not introduced universal childhood varicella immunization (UVI).

**Methods** A retrospective analysis was conducted on hospital discharge records contained in the national database of the Ministry of Health for the period January 2001–December 2013. The comparison of hospitalization rates of "pilot" versus "not pilot" regions was performed taking into account as "pilot" regions the three that first introduced UVI (Sicily, Veneto, and Apulia). The average annual percentage change in hospitalization rates was used to highlight any significant change in time trends.

**Results** In the period 2001–2013, 93,808 HZ-related hospitalizations were registered altogether. Complicated HZ was diagnosed in 53.2% of cases; a relevant part (32.5%) of hospitalizations involved subjects with at least one co-morbidity. In the three Italian "pilot" regions, a greater decrease of HZ-related hospitalization rates occurred in comparison to other regions.

**Discussion** A good understanding of the epidemiology of HZ disease is required to assess the overall impact of the varicella immunization programs and to establish the most appropriate health strategies against HZ.

**Conclusions** The data obtained confirm the epidemiological impact of HZ and its complications and the need of a preventive approach.

**Keywords** Herpes zoster · Hospitalizations · Temporal trends · Varicella vaccination

## Introduction

Herpes zoster (HZ) is the clinical manifestation of the reactivation, after several years or decades, of the varicella-zoster virus (VZV), latent in the sensory nerve ganglia after primary infection (chickenpox). Viral reactivation is due to a multifactorial process, closely related to VZV-specific cell-mediated immunity (CMI) [1], which tends to decrease with increasing age [2].

The risk of developing HZ and the degree of severity of the disease are almost unpredictable; however, in addition to aging, the female gender, race, mechanical trauma, exposure to immunotoxic chemicals, and some chronic conditions are considered as risk factors. Chronic conditions include chronic obstructive pulmonary disease (COPD), major depression, and other medical conditions requiring immunosuppressive treatment and/or involving immunosuppression [3]. The risk of HZ is estimated to be equal to 10–30% with a dramatic increase in incidence with age [4]; HZ affects up to 50% of subjects older than 85 years.

With the growing aging population, a rise in the number of cases of HZ in the near future is expected; this disease will become a public health issue [5–7].

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HZ is a potentially serious and debilitating condition characterized by unilateral vesicular rash that usually involves a single dermatome and may be accompanied by pain. Post-herpetic neuralgia (PHN) is the most common complication and affects 10–20% of patients with HZ; it is characterized by pain along cutaneous nerve endings that persists for more than 90 days after the disappearance of the rash [8]. PHN can have a devastating impact on quality of life of patients [9]. HZ can also affect the cranial nerves, especially the ophthalmic branch of the trigeminal nerve (ophthalmic HZ: HZO). HZO is associated with a variable risk of eye complications (range 30–78%); in 6% of cases, it is followed by a permanent reduced vision [10].

In immunocompromised patients, particularly in those with cellular immune deficiency, HZ can take a more severe clinical course [2].

HZ-related hospitalization rates vary widely around the world, ranging between 2 and 25/100,000 person-years reflecting different selection criteria in studies. Hospitalizations with HZ as principal diagnosis account for about 29–42% of HZ-related hospitalizations [4].

Independently from the geographical area investigated, hospitalizations proportionally increase with increasing age and the majority of HZ-related admissions occur in adults aged  $\geq 50$  years, ranging between a minimum of 10 hospitalizations per 100,000 persons in the age class 60–69 years to a maximum of 100 admissions per 100,000 in  $>80$ -year-old subjects [11–13].

In Italy, the actual number of HZ cases is underestimated due to the absence of a specific notification system; available information are derived from studies conducted in different and not always homogeneous health districts and/or geographical areas.

In Italy, with about 24.2 million people  $>50$  years of age, estimated 157,000 new cases of HZ occur each year, with an annual incidence of 6.3 per 1000 person-years; 73% of incident cases involve subjects  $>50$  years of age [14]. One study, conducted through a network of general practitioners (GPs), observed that 86.2%, of 413 enrolled  $>50$ -year-old subjects affected by HZ, reported HZ-related pain; in 20.6 and 9.2% of these patients, though treated within the first 72 h after symptoms' onset, PHN was present at 3 and 6 months [15]. According to a recent Italian study, conducted in the period 2013–2015, the clinical charts of 56 GPs working in four Italian regions (Liguria, Puglia, Toscana, and Veneto) reported an incidence of 6.42 (IC95% 5.93–6.95) HZ cases per 1000 person-years. In total, 22.7, 12.7, and 2.4% of HZ cases suffered PHN at 1 and 3 months and 1 year from the onset of acute episode, respectively [16].

However, an analysis of hospital discharge records (HDR) conducted in 1999–2005 reported an average of 4503 admissions per year; 62% involved  $>65$ -year-old

subjects [17]. A more recent study conducted in Tuscany confirmed the relevant epidemiological impact of HZ with an annual average of 368 admissions in the period 2002–2012. Many hospitalizations (68%) involved  $>65$ -year-old subjects; 51.2% of hospitalizations included cases with complications, among which the most frequent were neurological (24.2%) and ophthalmic (16.5%) ones [18].

As outlined in the Italian National Vaccination Plan (PNPV) 2012–2014 [19], some “pilot regions” (Sicily, Veneto, Apulia, Tuscany, Basilicata, Calabria, Sardinia, and Autonomous Province of Bolzano), have introduced universal childhood varicella immunization (UVI), achieving good coverage rates with a significant impact on both incidence and hospitalizations due to the disease [20]. Regarding the effects of UVI on the epidemiology of HZ in adults, despite the absence of consistent data, some authors believe the fundamental role of exogenous booster for maintaining the VZV-specific CMI [4].

The aim of this study was to estimate the HZ-related hospitalization rates in Italy in the period 2001–2013, and to evaluate the trend of hospitalizations during time pointing out any differences between regions that have or have not introduced UVI, taking into account that only a small proportion of HZ cases is hospitalized and hospitalizations for HZ represent only a part of the overall epidemiologic burden of the disease.

## Materials and methods

A retrospective analysis was conducted on HDRs contained in the national database of the Ministry of Health for the period January 2001–December 2013; the Italian resident population was taken into account as reference population (59.3 million inhabitants per year). HDRs' database was officially established in 1991 (Decree of the Ministry of Health, 28 December 1991) with the goal to briefly summarize the main information contained in the medical records. HDRs contain information about each patient discharged from public and private hospital institutions and include information related to both clinical and organizational aspects of each hospitalization. The coding of clinical information included in each HDR is performed using the international ICD-9-CM (International classification of disease, 9th revision, clinical modification) coding system, currently used in Italy.

Hospitalizations for HZ were obtained by selecting any of the six fields of the HDR diagnosis codes classified as follows: HZ with neurological complications, HZ with ophthalmic complications, HZ with other specified complications, HZ with other unspecified complications, and not complicated HZ (Table 1). We evaluated PHN when it was

**Table 1** ICD-9-CM codes used for the evaluation and classification of HZ cases

053.0	HZ with meningitis	HZ with neurological complications
053.1	HZ with other nervous system complications	
053.10	HZ with unspecified nervous system complication	
053.11	Geniculate HZ	
053.12	Post-herpetic trigeminal neuralgia	
053.13	Post-herpetic polyneuropathy	
053.14	HZ myelitis	
053.19	HZ with other nervous system complications	
053.2	HZ with ophthalmic complications	HZ with ophthalmic complications
053.20	HZ dermatitis of eyelid	
053.21	HZ keratoconjunctivitis	
053.22	HZ iridocyclitis	
053.29	HZ with other ophthalmic complications	
053.7	HZ with other specified complications	HZ with other specified complications
053.71	Otitis externa due to HZ	
053.79	HZ with other specified complications	
053.8	HZ with unspecified complication	HZ with other unspecified complications
053.9	HZ without mention of complication	HZ without complications

mentioned as a reason for hospital admission, regardless of the definition used.

The following medical conditions considered potentially associated with an increased risk for HZ have been identified [3, 21]: malignant neoplasms (ICD-9-CM code: 140–209), COPD (ICD-9-CM: 491–496), kidney diseases (ICD-9-CM: 580–588, 591), diabetes mellitus (ICD-9-CM code: 250), and autoimmune diseases (systemic lupus erythematosus codes ICD-9-CM: 710.0, 695.4, rheumatoid arthritis code ICD-9-CM: 714, and Sjogren’s syndrome ICD-9-CM code: 710.2). Hospitalizations for PHN were evaluated using the ICD-9-CM codes 053.12 and 053.13.

The annual hospitalization rates as well as rates stratified by age were calculated by dividing the annual number of HZ-related hospitalizations for the annual population provided by the National Statistics Institute (ISTAT) (per 100,000 inhabitants). The average length of stay was calculated for all cases as well as for the type of admission (hospitalization and day-hospital admission).

The comparison of hospitalization rates of “pilot” versus “not pilot” regions was performed taking into account as “pilot” regions only the three that first introduced UVI (Sicily in 2003, Veneto in 2005 and Apulia in 2006). Other five regions introduced UVI later (Tuscany in 2008, Basilicata and Calabria in 2010, Sardinia in 2011 and Friuli Venezia Giulia in 2013) [22]. This choice was taken to evaluate: (1) periods as much as possible overlapping and comparable; (2) regions with high vaccination coverage rates achieved in children at 24 months of age. Noteworthy, coverage rates were equal to 40% in 2003 and 84.5% in 2012 in Sicily, 68% in 2006 and 87.8% in 2012 in Veneto, and 49% in 2008 and 91.1% in 2012 in Apulia [21]. All other regions

were considered as “not pilot” ones. The description on when and how UVI has been introduced in some other Italian regions has been described elsewhere [23–25].

The average annual percentage change (AAPC) in hospitalization rates was used to highlight any significant change in time trends. Given a fixed interval of time, the AAPC is a synthetic measure of trend; an AAPC equal to zero supports the hypothesis of a constant trend, without any increase or decrease [26]. The 95% confidence intervals (95% CI) were calculated and a *p* value <0.05 was considered statistically significant.

Statistical analyses were performed using the software Epi-Info 2000 (Center for Disease Control and Prevention, Atlanta, GA, USA) and Joinpoint Regression Program, rel. 4.0.4. (Statistical Research and Applications Branch, National Cancer Institute, USA).

## Results

In the period 2001–2013, 93,808 HZ-related hospitalizations were registered altogether; 47,198 (50.3%) and 46,610 (49.7%) of these had HZ as principal and secondary diagnoses, respectively. The 55% of hospitalizations were registered in women (51,545 cases).

The analysis of data stratified by age showed that the number of hospitalizations increases along with age. As a matter of fact, 16.1% (15,089 admissions), 27.6% (25,968), and 56.3% (52,751) were registered in <49, 50–69, and >70-year-old subjects, respectively.

Most admissions (88.6%; 83,080 cases) were ordinary hospitalizations, and 11.4% (10,720) were day-hospital

admissions. The annual average was equal to 6391 and 825 hospitalizations and day-hospital admissions, respectively.

Overall, the average hospital length of stay was equal to  $21.3 \pm 25.0$  days. A total of 1271 (1.4%) subjects died during hospitalization; these deaths were due to other intercurrent co-morbidities and not to HZ disease.

Complicated HZ was diagnosed in 53.2% of cases (49,918) and was more frequent in subjects whose hospitalization has been codified as primary rather than secondary diagnosis (52.6 versus 40.9%, respectively,  $p < 0.01$ ). The most frequent complications were neurological (21,866; 23.3%), followed by ophthalmic (12,542; 13.4%) ones; the remaining 10.1% of cases (9482) involved HZ with other complications (specified or unspecified).

A relevant part (32.5%) of hospitalizations involved subjects with at least one co-morbidity; co-morbidities were significantly higher in hospitalizations with HZ in

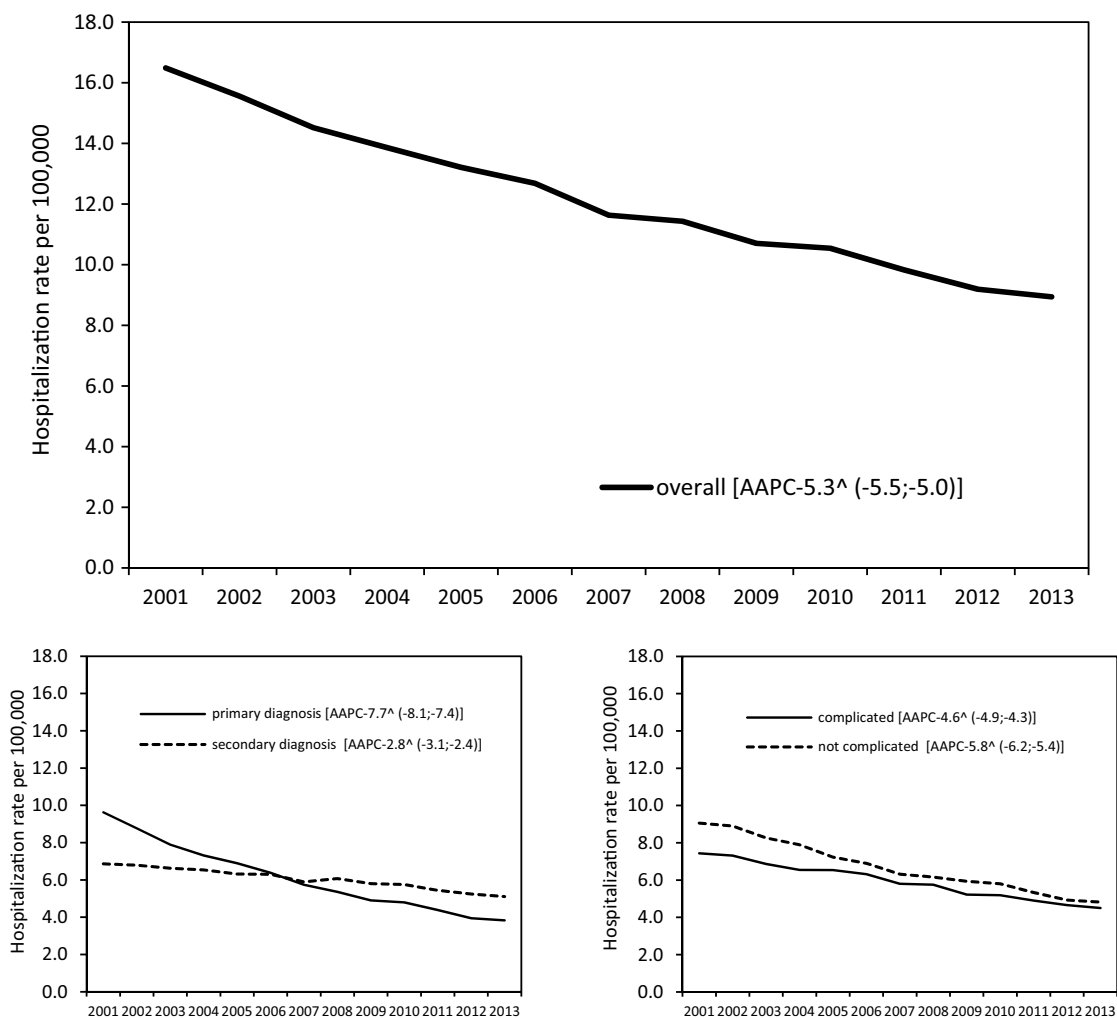
secondary than those in primary diagnosis (41.5% versus 23.6% respectively,  $p < 0.01$ ). In particular, HZ was associated with malignancies, diabetes, COPD, kidney failure, and autoimmune diseases in 11.4% (10,707), 10.8% (10,168), 7.9% (7370), 5.3% (4935), and 1.5% (1436) of cases, respectively (Table 2).

Stratifying co-morbidities by age group, a higher rate was registered in 70–79 and >80-year-old subjects with the exception of malignancies that had a peak in the <18 and 50–69 year age groups.

As a whole, during the studied period, the rate of HZ-related hospitalizations was equal to 12.1/100,000 inhabitants/year. The temporal trend and, in particular, the average annual percentage change showed a gradual and significant reduction of hospitalizations from 16.5 in 2001 to 8.9/100,000 in 2013 [AAPC  $-5.3^{(-5.5;-5.0)}$ ] (Fig. 1).

**Table 2** Main characteristics of subjects discharged with an HZ diagnosis (Italy, 2001–2013)

	Primary diagnosis, <i>n</i> (%)	Secondary diagnosis, <i>n</i> (%)	Total
	47,198 (50.3)	46,610 (49.7)	93,808
Gender, <i>n</i> (%)			
Male	21,545 (45.6)	20,718 (44.4)	42,263 (45.1)
Female	25,653 (54.4)	25,892 (55.6)	51,545 (54.9)
Age class, <i>n</i> (%)			
<18	2091 (4.4)	912 (2.0)	3003 (3.2)
18–49	6431 (13.6)	5655 (12.1)	12,086 (12.9)
50–59	5160 (10.9)	4000 (8.6)	9160 (9.8)
60–69	9018 (19.1)	7790 (16.7)	16,808 (17.9)
70–79	13,495 (28.6)	13,596 (29.2)	27,091 (28.9)
80+	11,003 (23.3)	14,657 (31.4)	25,660 (27.4)
Average length of stay, average (SD)	15.6 (13.3)	27.0 (31.8)	21.3 (25.0)
Discharge, <i>n</i> (%)			
Alive	47,060 (99.7)	45,477 (97.6)	92,537 (98.6)
Dead	138 (0.3)	1133 (2.4)	1271 (1.4)
Type of hospitalization, <i>n</i> (%)			
Ordinary hospitalization	41,669 (88.3)	41,419 (88.9)	83,088 (88.6)
Day-hospital admission	5529 (11.7)	5191 (11.1)	10,720 (11.4)
HZ, <i>n</i> (%)			
Uncomplicated	22,377 (47.4)	27,541 (59.1)	49,918 (53.2)
With complications	24,821 (52.6)	19,069 (40.9)	43,890 (46.8)
Neurological	12,052 (25.5)	9814 (21.1)	21,866 (23.3)
Ophthalmic	7431 (15.7)	5111 (11.0)	12,542 (13.4)
Other specified complications	3606 (7.6)	2397 (5.1)	6003 (6.4)
Other unspecified complications	1732 (3.7)	1747 (3.7)	3479 (3.7)
Co-morbidity, <i>n</i> (%)			
Malignancy	3092 (6.6)	7608 (16.3)	10,700 (11.4)
COPD	2387 (5.1)	4983 (10.7)	7370 (7.9)
Kidney failure	1514 (3.2)	3421 (7.3)	4935 (5.3)
Diabetes	4736 (10.0)	5432 (11.7)	10,168 (10.8)
Autoimmune diseases	655 (1.4)	781 (1.7)	1436 (1.5)



<sup>^</sup>p<0.05

**Fig. 1** Temporal trend of HZ-related hospitalizations; total cases and cases stratified by diagnosis and possible complications

A statistically significant reduction in the rate of hospitalization was confirmed taking into account the type of diagnosis (primary or secondary) as well as the presence/absence of complications. In particular, with reference to the type of diagnosis, the decrease was higher for hospitalizations with a principal diagnosis of HZ, which changed from 9.6 in 2001 to 3.8/100,000 inhabitants in 2013 [AAPC  $-7.7^{(-8.1;-7.4)}$ ], instead HZ as secondary diagnosis changed from 6.9 to 5.1 in the same period [AAPC  $-2.8^{(-3.1;-2.4)}$ ]. Taking complications into account, a greatest reduction in trend was recorded in hospitalizations with uncomplicated diagnosis of HZ, which moved from 9.1 in 2001 to 4.8/100,000 inhabitants in 2013 [AAPC  $-5.8^{(-6.2;-5.4)}$ ] (Fig. 1).

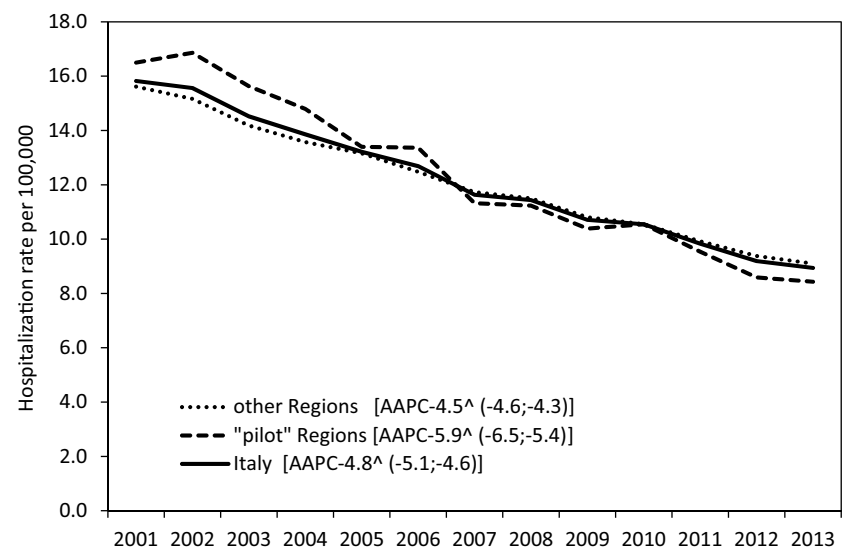
Comparing the rates of HZ-related hospitalization in the “pilot” versus other regions, the temporal trend significantly decreased in both groups; however, the “pilot”

regions experienced a greater reduction:  $\downarrow 48.9\%$  ( $\downarrow 45.2;$   $\downarrow 52.4$ ) versus  $\downarrow 41,7\%$  ( $\downarrow 39.4;$   $\downarrow 43.9$ ) respectively. Since 2007, a consistently lower rate of hospitalizations has been registered in the “pilot” regions (Fig. 2).

In the studied period, 6580 hospitalizations with a diagnosis of PHN were registered (7.0% of all hospitalizations included in the analysis). The proportion of admissions due to PHN increased with age, reaching around 9% in subjects older than 70 years in both genders (Fig. 3). The main clinical characteristics of hospitalized subjects with PHN are summarized in Table 3. Most admissions due to PHN (78.3%; 6546 cases) were ordinary hospitalizations, while 21.7% (1427) of them were day-hospital admissions. The annual average was equal to 396 hospitalizations and 110 day-hospital admissions, respectively.

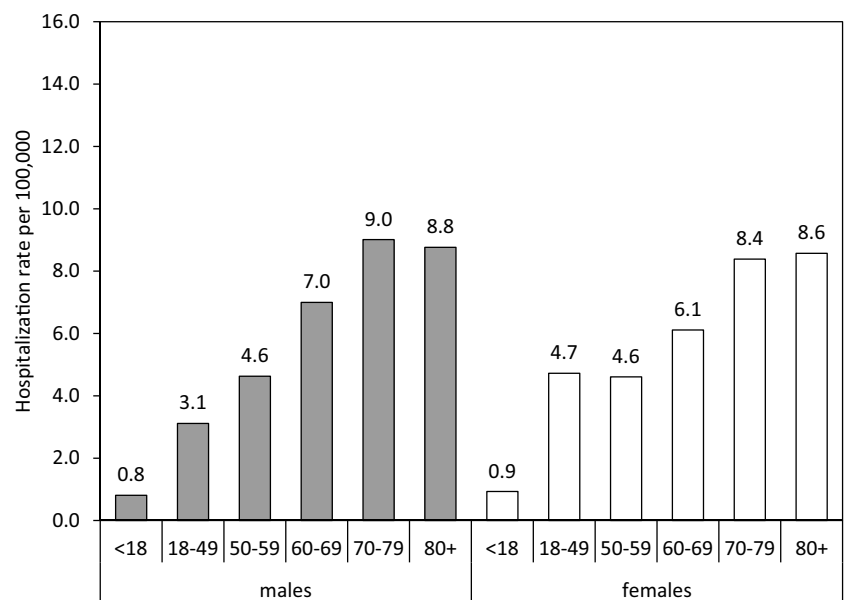
Hospitalization due to PHN was related to diabetes, COPD, and malignancies in 10.6, 8.3, and 7.1% of cases,

**Fig. 2** Temporal trend of HZ-related hospitalizations; “pilot” versus “not pilot” regions



$p < 0.05$

**Fig. 3** Rate of hospitalizations due to post-herpetic neuralgia, stratified by gender and age



respectively. The percentage of co-morbidity increased with age.

## Discussion

A good understanding of the epidemiology of HZ disease is required to assess the overall impact of the varicella immunization programs and to establish the most appropriate health strategies against HZ. An indicator to be used is given by hospital admissions related to this disease, which express the most serious cases. The purpose of this study was to evaluate the national impact of HZ in terms of

hospital admissions. As for the gender of the studied subjects, it was confirmed, compared to the literature, a higher rate of hospitalizations in the female population. To explain this difference, it has been suggested a different use of the health care system by females or a higher susceptibility to the reactivation of VZV in women [27]. On the other side, accordingly to exogenous boosting theory, women could be less prone to develop HZ because of their relevant “mixing pattern” (being mothers and/or grandmothers) with children possibly affected by varicella [28].

It was also confirmed an age-related increase in hospitalizations, particularly in >70-year-old subjects, in both genders. Age represents a risk factor for HZ, due to the decline

**Table 3** Main characteristics of subjects discharged with a diagnosis of post-herpetic neuralgia (Italy, 2001–2013)

	Primary diagnosis, <i>n</i> (%)	Secondary diagnosis, <i>n</i> (%)	Total
	3408 (51.8)	3172 (48.2)	6580
Average length of stay, average (SD)	16.6 (19.1)	24.9 (26.0)	20.6 (23.1)
Discharge, <i>n</i> (%)			
Alive	3401 (99.8)	3145 (99.1)	6546 (99.5)
Dead	7 (0.2)	27 (0.9)	34 (0.5)
Type of hospitalization, <i>n</i> (%)			
Ordinary hospitalization	2435 (71.4)	2718 (85.7)	5153 (78.3)
Day-hospital admission	973 (28.6)	454 (14.3)	1427 (21.7)
Co-morbidity, <i>n</i> (%)			
Malignancy	111 (3.3)	355 (11.2)	466 (7.1)
COPD	170 (5.0)	375 (11.8)	545 (8.3)
Kidney failure	92 (2.7)	192 (6.1)	284 (4.3)
Diabetes	306 (9.0)	394 (12.4)	700 (10.6)
Autoimmune diseases	35 (1.0)	54 (1.7)	89 (1.4)

in VZV-specific cell-mediated immunity. Besides, in older subjects, the likelihood of being hospitalized increases because of the outcome of the therapy in use, the need of a more effective control of HZ-related pain, or the increased frequency of relapses [29]. The progressively aging population is undoubtedly a broad and problematic issue that the health system has to cope with. In 2050, more than a third of the Italian population will be >65 years; so it will increase the prevalence of chronic diseases such as diabetes, malignancies, cardiovascular diseases, and neurodegenerative diseases, and more and more resources will be needed to ensure adequate care for citizens.

Several studies have confirmed the relationship between HZ and chronic diseases; a retrospective cohort study of 55,492 patients with an average age of 60 years found that patients with diabetes mellitus, kidney failure, cancer, and other conditions have a risk of develop HZ 1.8–8.4 times higher than patients with other diseases [30]. Some evidence suggests that sometimes, the presence of HZ can be a sign of an underlying malignancy. As a matter of fact, a higher incidence of malignancy has been registered in patients with HZ in comparison to healthy controls; a higher risk of onset of cancer has been reported about 6 months after the diagnosis of HZ (hazard ratio 1.19) [31]. In addition, this study has evaluated the presence of specific chronic diseases, probably related to an altered CMI, which may lead to an increase of HZ cases. The results of the present analysis, in line with other authors, point out that HZ is associated with a high frequency to malignant neoplasms, diabetes, and COPD. Subjects with underlying chronic medical conditions are fragile patients with a higher relative risk of suffering from HZ in comparison to healthy people of the same age. Besides, they have an increased risk of imbalance of the underlying chronic

disease because of HZ with a greater frequency and severity of HZ-related complications. The analysis of the ICD-9-CM codes showed that nearly half of HZ-related hospitalizations have complications. The most frequent were neurological (23.3%) and ophthalmic (13.4%) complications that significantly impact on daily activities (work, household activities, hobbies, etc.) of both the patients and their families.

Accordingly, to some authors [28], exogenous exposure to the virus through individuals affected by chickenpox or shingles could play a role as a booster for VZV-specific CMI and thus could decrease the risk of HZ. Extensive vaccination for chickenpox, reducing the spreading of VZV in the community and, therefore, eliminating the exogenous boosters, could increase the incidence of HZ in the unimmunized population (adults, elderly). In the literature, however, coherent and consistent evidence of the correlation between UVI and an increased incidence of HZ is lacking. Moreover, some authors have reported an increasing trend of HZ incidence already started in the pre-immunization era and, therefore, not attributable to the introduction of vaccination [32–39]. In Italy, between 2001 and 2013, there was a significant decrease in the rate of hospitalizations for all causes. A similar decreasing trend has been also described for both HZ and complicated HZ; this decrease, consistent with the national trend, has been induced by the reduction of inappropriateness of admissions and by the change of care settings in place in our country [40]. In particular, the analysis of the temporal trend showed that in the three Italian “pilot” regions that first introduced UVI, a greater significant decrease of HZ-related hospitalization rates occurred in comparison to other regions.

Our study has some limitations. It is not easy to estimate the morbidity of HZ in the general population. This

is partly because the currently available epidemiological picture is still hazy due to differences in study design and population profiles, as well as in access to health care and recording methods. In particular, HDRs database is designed for administrative purposes and coding errors in hospital discharge records are possible. Using only discharge diagnosis method for epidemiological evaluations of infectious diseases can result in an underestimation of sensitivity and timeliness, but hospital discharge data can prove useful for assessing the cases severe enough to warrant hospitalization [41]. Besides, in addition to the previous points, limiting the evaluation to three pilot regions on 20 Italian regions could have decreased the value of our analysis; on the other hand, acting in this way has probably allowed us to be as conservative as possible and to avoid including severe bias in our research. The strengths of our work lie in having designed our retrospective cohort study to investigate the trend of HZ-related hospitalizations in Italy, by means of data routinely collected by the public health service allowing the analysis of wide geographic areas and long time periods. The analysis of routinely available records can prove an efficient method for monitoring trends in the state of health of populations.

In conclusion, even if only a small proportion of HZ cases is hospitalized and hospitalizations for HZ represent only a part of the overall epidemiologic burden of the disease, our data confirm that the epidemiological and clinical (and also economic) impact of this relevant infectious disease makes prevention of HZ absolutely essential. Nowadays, a live attenuated virus vaccine, with a high antigen content, has been licensed for the use in subjects >50 years of age in Europe (and >60 years in USA). The high antigen content permits to adequately stimulate CMI and has a good level of efficacy (particularly against PHN), safety, and tolerability [42, 43]. Evidence confirms the promising impact of the HZ vaccine on the incidence of HZ and PHN observed in the post-licensure clinical trials in “real-world” settings [44–46]. In particular, the vaccine’s good safety and tolerability profile have been confirmed in all available studies, suggesting the existence of a potential benefit of HZ vaccine also in not severely immunosuppressed patients and in individuals with selected immune diseases with a good safety profile [47].

Recently, an ad hoc population model has been developed to value the clinical and economic impact of HZ vaccination program for the elderly in Italy. The result show that the vaccination in elderly could have a relevant impact on the reduction of clinical cases and a favorable economic profile for the National Health Service (NHS) [48]. Immunization would reduce the overall health and social impact of this disease and would allow to improve the well-being of the population, of elderly in particular [49].

## Compliance with ethical standards

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

**Ethical approval** HDRs were provided by the National Archive of SDO data, Ministry of Health, General Directorate of Healthcare Planning, VI Office. For this type of retrospective study, formal consent is not required.

**Conflict of interest** Giovanni Gabutti and Vincenzo Baldo received grants from Sanofi Pasteur MSD, GSK Biologicals SA, Novartis, Crucell/Janssen, Pfizer, Sequirus, Merck Italy, and Sanofi Pasteur for taking part to advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses and as principal investigator and chief of O.U. in RCTs. Rosa Prato has served in advisory committees related to herpes zoster vaccine for Sanofi Pasteur MSD; she also reports grants and nonfinancial support from Sanofi Pasteur MSD, Pfizer, GSK, and Novartis, outside this work. Domenico Martinelli reports grants and nonfinancial support from GSK, Pfizer, and Sanofi Pasteur MSD, outside this work. Nicoletta Valente, Silvia Cocchio, Armando Stefanati, and Tatjana Baldovin do not have any conflict of interest.

**Statement of human and animal rights** HDRs were provided by the National Archive of SDO data, Ministry of Health, General Directorate of Healthcare Planning, VI Office. Accordingly to the current regulations, a specific permit by an Ethical Committee was not necessary, as no personal data were available and only anonymous unlinked aggregated data were analyzed. This study was performed in compliance to the Helsinki Declaration as well as to the Italian law (Decree n. 196/2003 for the protection of personal data).

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