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Impact of postherpetic neuralgia: A six year population-based analysis on people aged 50 years or older

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SUMMARY

Objectives: To estimate the incidence and burden of postherpetic neuralgia (PHN) and to investigate risk factors for PHN in the Valencia Region of Spain.
Methods: Data were extracted from population and healthcare databases from the Valencia Region (2009–2014). Herpes zoster (HZ) and PHN were defined using ICD-9 codes and drug prescriptions in people aged ≥50 years. The risk of HZ patients for developing PHN and potential risk factors (diabetes mellitus, COPD and heart failure) were investigated. A survival analysis was developed to estimate the cumulative hazard of developing HZ and PHN between ages 50–90 years.
Results: From a total of 2,289,485 subjects, 87,086 cases of HZ were registered, 13,658 (15.7%) of whom developed PHN. PHN risk was higher in women and increased sharply with age and comorbidities as diabetes mellitus, COPD and heart failure. The cumulative risk of developing HZ between ages 50–90 years was 31.7% (95% CI: 31.3-32.1) and 6.9 (95% CI: 6.7–7.1) for PHN.
Conclusions: PHN risk was higher in women and increased with age and comorbidities. At least 32% and 7% of people will develop HZ and PHN, respectively, between ages 50–90 years. These results should be considered for vaccine policy implementation.

Introduction

Herpes zoster (HZ) and its main complication, postherpetic neuralgia (PHN), constitute an important health problem, reducing the quality of life of patients, and increasing healthcare costs.[1] Many patients with PHN develop severe physical, occupational and social disabilities because of enduring pain.[2] HZ or shingles is caused by the reactivation of the Varicella Zoster Virus (VZV), which remains latent in sensory nerve ganglia following the primary infection (chickenpox). This reactivation causes a localized eruption of vesicular lesions and the presence of pain and inflammation of the affected nerve root.[3] Definitions of PHN vary among authors, "a dermatomal pain that persists at least 90 days after the appearance of the acute HZ rash" being the most commonly accepted.[4]

HZ incidence increases sharply with age, being the highest after the age of 50.[5,6] Apart from age, underlying diseases such as diabetes, congestive heart failure (HF) or chronic obstructive pulmonary disease (COPD) seem to increase the risk, severity and impact of zoster episodes on senior population.[7–9] The systemic administration of antivirals within 72 h of the onset of rash may reduce inflammation and severity of symptoms of the HZ. However, PHN is a challenging condition to treat and there is not consistent evidence that administering antivirals at rash onset reduces PHN risk.[9,10] Topical anesthetics, antiepileptics, tricyclic antidepressants and, lastly, opioid analgesics as tramadol are usually prescribed.[4] However, in many cases PHN management is unsatisfactory and patients end up going to pain specialists.

Vaccinations represent an important preventive tool against infections. Since 2006, a live-attenuated vaccine for the prevention of HZ (Zostavax, Merck, Sanofi Pasteur) has been licensed in many countries for the use in adults older than 50 years of age.[11,12] The Shingles Prevention Study (SPS) demonstrated that the use of the zoster vaccine reduced the burden of HZ by 61.1%, and the incidence of PHN by 66.5%.[11,12] A recent study from the United States

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demonstrated that vaccine effectiveness was higher and better preserved over time for PHN than for community HZ.[13] Currently in Spain, there are efforts to introduce recommendations for HZ vaccination. Given the relatively high cost of the zoster vaccine the identification of populations with underlying diseases at increased risk for HZ and PHN constitutes an important research question to allow health authorities to make decisions on HZ-PHN immunization policies.[9]

The annual incidence of HZ reported in a previous population-based study in our Region was 8.60 cases/1000 persons ≥50 years,[6] however, data on the epidemiology of PHN in Spain are scarce. A previous prospective study (14) that followed up 130 cases of HZ for a year showed that 14.5% of patients with a HZ experienced persistent pain for at least 3 months after the HZ.

The present study has been designed to provide additional data on the burden of PHN in Spain. It aims to estimate the incidence of PHN, the proportion of HZ patients developing PHN and to identify risk factors for PHN in general population older than 50 years through a population-based study using databases of the Valencia Region. A secondary objective was to estimate the cumulative risk of developing HZ and PHN for population aged 50–90 years and the total number of primary care visits required for HZ and PHN management.

Methods

Using an observational, population-based study, the incidence and burden of PHN were estimated from 1st of January 2009 until 31st of December 2014 using healthcare databases from the Valencia Region, Spain.

Setting and study population

The Valencia Region of Spain has a population of approximately 5 million inhabitants.[15] Over 98% of them are insured by the Regional Health System (RHS),[16] which consists of 24 Health Departments.[17] Each of them includes at least one hospital, one specialties center and a number of ambulatory centers. All primary care visits and hospitalizations are recorded in clinical databases.

About 37% of the Valencian population is 50 years of age or older. The study cohort included all individuals aged 50 years or older, living in the Valencia Region and insured by the RHS between the 1st of January 2009 and the 31st of December 2014. Subjects were included in the cohort if they were aged 50 years or older on 1st January 2009, or on the day of entry into RHS, or on their fiftieth birthday, whichever occurred last. Follow-up ended when they left Valencia (data of deletion from RHS), on their death or at the end of the study (31 December 2014), whichever occurred first. Patients with immunosuppressive conditions diagnosed before the beginning of the follow-up period were excluded (determined by the presence of a diagnostic International Classification of Diseases 9th Clinical Modification [ICD-9-CM] code for Human immunodeficiency virus [HIV], organ transplantation, cancers, immunodeficiency disorders or autoimmune diseases).[18] If a subject developed one of the aforementioned immunosuppressive conditions during the follow-up period, they were excluded from the study at this point.

Data source: electronic databases

Primary care electronic medical notes were implemented in 2006 (SIA) and all medical contacts (visits), with ICD-9-CM recorded diagnoses are registered.[17] For hospitalization we used the hospital discharge database, MBDS (minimum basic data set), where discharge diagnoses are ICD-9-CM coded. Care Provision Management (GAIA) is a medication information system available to all those professionals involved in prescription and dispensation, created by the Department of Health. Data from these databases can be linked through a unique personal identification number (SIP).[6]

Case definitions

An incident case of HZ was defined as the first appearance of a HZ-related ICD-9-CM code (053.*), in either SIA or MBDS (in any diagnostic position). Although our study period started on the 1st of January 2009, registers from 1st of January 2007 were available so we ensure the codes represented incident cases. Any outpatient medical contact or visit, or hospital admission related to HZ was considered as a medical encounter. A recurrent HZ case was considered when an ICD-9 code for HZ appeared after 6 months or more after a previous HZ encounter. The positive predictive value (PPV) of the diagnostic code in these databases is 92.7%; 95% CI 89.1–95.4.[6]

For comparison purposes with previous studies, PHN was defined as pain persisting beyond the acute phase of an HZ considering periods from 30 (PHN1), 90 (PHN3) and 150 (PHN5) days post HZ diagnosis, however only pain persisting beyond 90 days is considered true PHN. PHN cases were defined using the following criteria: (1) the presence of an ICD-9 code for HZ followed by an ICD-9 code indicative of PHN (053.12, 053.13 or 053.19) within the defined periods (30–180, 90–180 and 150–180 days post HZ), or (2) the presence of an ICD-9 code for HZ followed by a prescription consistent with PHN (Supplemental Table 1) during the defined periods, or (3) the presence of an ICD-9 code for HZ followed by an ICD-9 code for chronic pain (338.2) during the defined periods. All the codes were searched in outpatient and hospital databases (SIA and MBDS).

Variables

Birth date, gender, nationality, urban/rural residence, social exclusion risk and health department were recorded for each person. Rural residence was classified based on the law for sustainable development of the rural environment by the Regional Government. Rural areas were classified according to: population density (less than 100 inhabitants per km^2), urban nucleus proximity, population trend, percentage of employment in primary, secondary and tertiary sectors and territorial structure. Social exclusion risk was obtained from electronic database (SIP) where its classification is based on aspects such as unemployment, non-citizen in irregular situation or without resources.[17]

Diabetes, HF and COPD were included also as co-variables. Their status was identified when a diagnostic ICD-9 code for diabetes (250.*), for HF (428-428.9) or for COPD (491, 492 or 496) was activated in SIA or in any CMBD position and when a prescription or dispensation for specific medication for diabetes or for COPD was detected in GAIA (insulin and/or oral anti-diabetic drugs and inhaled corticosteroids, respectively).

Statistical analysis

The proportion of HZ cases that developed PHN was calculated considering the three definitions (PHN1, PHN3 and PHN5). The PHN incidence rates (per person and year) and 95% CI were calculated by age, sex and calendar year using the Poisson exact method.

The risk to develop PHN in subjects with a previous HZ episode was modeled by a mixed Poisson regression, adjusted by gender, calendar year, age, comorbidities (diabetes, HF, COPD), health department and the group variable (corresponding with records from the database), the last two as random effects. The group variable

Table 1
Demographic characteristics for population ≥50 years old in the Valencia Region from 2009 to 2014 ($n = 2,289,485$).

	Total Cohort	HZ patients	PHN3 patients
Age (years)	N (%)	N (%)	N (%)
50–59	1,027,417	19,315	1872
60–69	881,947	23,273	3280
70–79	699,885	20,635	3958
≥ 80	414,036	13,445	2826
Gender			
Male	1, 061,732 (46%)	28,578 (38%)	3497 (30%)
Female	1, 227,753 (54%)	46,537 (62%)	8229 (70%)
Nationality	$N = 1,774,750$[a]	$N = 68,305$[a]	$N = 10,904$[a]
Spanish	1, 586,043 (89%)	64,723 (95%)	10449 (96%)
Other	188,707 (11%)	3,582 (5%)	455 (4%)
Urban status	$N = 2,261,243$[a]	$N = 75,018$[a]	$N = 11,725$[a]
Urban	2, 191,837 (97%)	72,557 (97%)	11360 (97%)
Rural	69,406 (3%)	2,461 (3%)	365 (3%)
Social Exclusion	$N = 1,739,725$[a]	$N = 68,052$[a]	$N = 10,875$[a]
Risk	202,365 (12%)	6,175 (9%)	851 (8%)
No risk	1, 537,360 (88%)	61,877 (91%)	10024 (92%)
Comorbidities			
Diabetes mellitus	397,940 (17%)	15,678 (21%)	3165 (27%)
COPD	161,317 (7%)	6,665 (9%)	1428 (12%)
Heart failure	103,240 (5%)	3,487 (5%)	850 (7%)
Total (%)	2,289,485	75,115 (3,3%)[b]	11,726 (0,5%)[b]

[a] Number of subjects with available information for each category.
[b] Percentages calculated considering total cohort (2,289,485) as 100%.

Table 2
Number of HZ and PHN cases and proportion of HZ cases developing PHN by age, gender and year.

	HZ cases	PHN1 cases (%)	PHN3 cases (%)	PHN5 cases (%)
	87086	19101 (21.9)	13658 (15.7)	8805 (10.1)
Age				
50–59	21045	2912 (13.8)	2017 (9.6)	1184 (5.6)
60–69	26124	5203 (19.9)	3658 (14.0)	2269 (8.7)
70–79	23930	6418 (26.8)	4580 (19.1)	3074 (12.9)
≥ 80	15987	4568 (28.6)	3403 (21.3)	2278 (14.2)
Gender				
M	32737	6082 (18.6)	4128 (12.6)	2573 (7.9)
F	54349	13019 (24.0)	9530 (17.5)	6232 (11.5)
Comorbidities				
No diabetes	68776	14087 (20.5)	9953 (14.5)	6364 (9.3)
diabetes	18310	5014 (27.4)	3705 (20.2)	2441 (13.3)
No COPD	79234	16778 (21.2)	11967 (15.1)	7671 (9.7)
COPD	7852	2323 (29.6)	1691 (21.5)	1134 (14.4)
No HF	83055	17812 (21.4)	12675 (15.3)	8094 (9.7)
HF	4031	1289 (32.0)	983 (24.4)	711 (17.6)
Year				
2009	15246	3191 (20.1)	2275 (14.9)	1411 (9.3)
2010	15409	3338 (21.7)	2461 (16.0)	1647 (10.7)
2011	15568	3290 (21.1)	2459 (15.8)	1649 (10.6)
2012	14669	3346 (22.8)	2439 (16.6)	1552 (10.6)
2013	13692	3285 (24.0)	2437 (17.8)	1650 (12.1)
2014	12502	2651 (21.2)*	1587 (12.7)*	896 (7.2)*

*PHN cases corresponding to HZ developed from January to July. Follow-up period for HZ cases developed after July of 2014 was not complete.

was considered in order to avoid the over-dispersion problem. Relative risk estimations are presented with 95% CI.

A survival analysis was developed to estimate the cumulative hazard (or cumulative risk) of developing HZ, PHN1, PHN3 and PHN5 from 50 to 90 years of age. The primary time variable for the survival analysis was defined as the age (in years) at entry into the study and the age at which subjects experience the HZ/PHN or their follow up is censored.

Total number of primary care visits registered for HZ cases and for HZ cases developing PHN (HZ–PHN) as well as the mean number of visits per HZ and per HZ–PHN case were estimated. The percentages of the total cases of HZ that were hospitalized, that received antivirals prescription, that were prescribed with PHN medication (Supplemental Table 1) and that caused sick leaves (population aged 50–69 years) were also calculated, as well as the mean duration of sick leaves in days. Follow-up period for each HZ case was 6 months from HZ code appearance or until the end of the study period, whichever occurred first.

Ethical considerations

The study protocol was approved by the Ethics Committee of Dirección General de Salud Pública / Centro Superior de Investigación en Salud Pública, which allowed for the linkage of the different databases by the administrators database using a codified SIP number.

Results

A total of 2,289,485 subjects were included in the study. From this cohort, 87,086 cases of HZ were registered in 75,115 patients, and 11,726 (15.6%) of them developed PHN3. Women represented 62% of the total HZ and 70% of the total PHN patients. The demographic characteristics of the population are shown in Table 1.

Table 2 shows the percentage of HZ cases that developed PHN for the three considered periods. Of the total cases of HZ, 21.9% met criteria for PHN1, 15.7% for PHN3 and 10.1% for PHN5. The proportion of HZ cases developing PHN was higher for cases occurring in women for all three definitions. 9.6% of HZ cases occurring in patients aged 50-59 resulted in PHN that persisted for at least 3 months (PHN3). This percentage increased with age until 21.3% for cases in elderly people (above 80 years old). 5.6% of HZ cases in patients aged 50–59 developed PHN that persisted for at least 5 months (PHN5), rising to 14.2% in cases occurring in people ≥ 80 years old. Patients with any of the studied comorbidities (COPD, diabetes or HF) were more likely to develop PHN than subjects without each of the comorbidities (Table 2).

Table 3 shows the incidence rates of PHN per person and year by age and gender. Overall incidence rate of PHN3 was 1.19/1000 persons-year and it was twice as high in women as in men (1.55 vs. 0.78/1000 persons-year, respectively). Supplemental Fig. 1 illustrates the incidence rates of PHN1, PHN3 and PHN5 per 1000 persons-year for populations with COPD, diabetes and HF by age groups. The adjusted risk of developing PHN (Table 4) was more than double for patients aged 60–69 years compared to patients aged 50–59 (Relative risks [RR] from 2 for PHN1 to 2.19 for PHN5) and approximately triple for patients 70–79 (RR from 2.84 to 3.45). The risk increased more sharply with age for PHN5 definition. Patients ≥ 80 years old had 3.67 times higher risk of developing PHN5. Patients with one of the three comorbidities were more likely to develop PHN than patients without each of the comorbidities (Table 4). Of them, COPD was the most strongly associated with PHN (RR from 1.86 to 1.95).

The cumulative risk of developing HZ up to the age of 90 years (considering from 50 years of age) was estimated to be 31.7% (95% CI: 31.3–32.1) (Fig 1). The risk of developing PHN1, PHN3 and PHN5 was 9.3 (95% CI: 9.0–9.5), 6.9 (95% CI: 6.7-7.1) and 4.7 (95% CI: 4.5–4.9), respectively.

During a follow-up period, the 87,086 cases of HZ generated a total of 175,028 primary care visits. Of them, 136,908 corresponded to HZ cases without PHN (mean per HZ case 1.87 SD = 1.4) and 38,970 were related to HZ-PHN cases (mean per HZ-PHN case 2.85 SD = 2.7). HZ without PHN and HZ–PHN cases received 23,323 (32% of the total HZ without PHN cases) and 4167 (31% of the total HZ-PHN cases) antiviral prescriptions, respectively. Of the PHN medication (Supplemental Table 1) 53% was prescribed for HZ cases without PHN (15,308 prescriptions) and 47% for HZ-PHN cases (13,583 prescriptions) according to our PHN3 definition. 1.2% of the

Table 3
Incidence rates of PHN (per 1000 persons-per year) by age groups and gender in the Valencia region in 2009–2014.

	PHN1			PHN3			PHN5		
Age (years)	Cases	IR	95% CI	Cases	IR	95% CI	Cases	IR	95% CI
50–59	2697	0,77	(0,75–0,80)	1833	0,53	(0,50–0,55)	1057	0,3	(0,29–0,32)
60–69	4666	1,62	(1,57–1,66)	3278	1,13	(1,10–1,17)	2019	0,7	(0,67–0,73)
70–79	5393	2,47	(2,41–2,54)	3870	1,77	(1,71–1,83)	2624	1,2	(1,15–1,24)
≥80	3732	2,81	(2,72–2,91)	2818	2,12	(2,04–2,20)	1981	1,49	(1,42–1,55)
≥50	16488	1,67	(1,64–1,70)	11799	1,19	(1,17–1,21)	7681	0,78	(0,76–0,79)
Gender									
Male	5260	1,16	(1,13–1,19)	3529	0,78	(0,75–0,80)	2189	0,48	(0,46–0,5)
Female	11228	2,1	(2,07–2,14)	8270	1,55	(1,51–1,58)	5492	1,03	(1–1,05)

*IR: Incidence Rate. CI: Confidence Interval.

Tabla 4
Relative risk estimates and 95% confidence intervals (95%CI) for the association between PHN incidence and gender, age, comorbidities and calendar year adjusted by health department as a random effect using a Poisson regression.

	RR (CI 95%)		
	PHN1	PHN3	PHN5
Gender			
M	1	1	1
F	1.78 (1.71–1.84)	1.94 (1.87–2.02)	2.07 (1.96–2.17)
Age			
50–59	1	1	1
60–69	2 (1.91–2.11)	2.05 (1.92–2.18)	2.19 (2.02–2.36)
70–79	2.84 (2.7–2.98)	2.95 (2.77–3.12)	3.45 (3.2–3.73)
80_+	2.85 (2.7–3.01)	3.08 (2.89–3.29)	3.67 (3.37–3.98)
Comorbidities			
Non-diabetes	1	1	1
diabetes	1.41 (1.36–1.47)	1.46 (1.4–1.53)	1.45 (1.37–1.52)
Non-COPD	1	1	1
COPD	1.86 (1.77–1.96)	1.88 (1.77–1.99)	1.95 (1.81–2.09)
Non-HF	1	1	1
HF	1.39 (1.3–1.48)	1.42 (1.31–1.53)	1.52 (1.38–1.66)
Year			
2009	1	1	1
2010	1.04 (0.99–1.1)	1.11 (1.04–1.19)	1.23 (1.13–1.33)
2011	0.99 (0.93–1.05)	1.08 (1.01–1.16)	1.3 (1.2–1.41)
2012	1.03 (0.98–1.09)	1.11 (1.04–1.19)	1.23 (1.13–1.33)
2013	1.07 (1.01–1.13)	1.12 (1.04–1.21)	1.23 (1.14–1.34)
2014	1.06 (1–1.12)	1.14 (1.06–1.22)	1.37 (1.25–1.47)

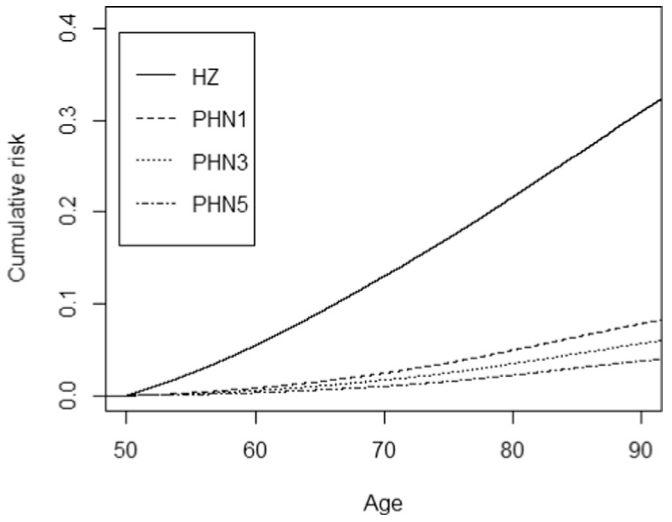

Fig. 1. Cumulative risk of developing HZ, PHN1, PHN3 and PHN5 from 50 to 90 years of age.

total cases of HZ (with and without PHN) were hospitalized and 2% caused sick leaves to population aged between 50–69 years, with a mean duration of 28.8 days (SD = 37).

Discussion

Since 2011,[14] no updates on the epidemiology and costs of PHN have been developed in Spain, apart from inferences or extrapolations on this issue.[19] The results showed in this retrospective study reflect the actual care of the entire population older than 50 years during the six year period analyzed. This is the largest population-based study addressing the PHN burden and its risk factors in Spain.

According to our data, 15.7% of the total HZ cases developed in people above 50 years old resulted in PHN lasting for at least three months after the acute phase of a HZ. These results are comparable to previous studies in the same Region of Spain,[14], which found an incidence of PHN3 of around 14.5%. Although they considered all patients older than 14 years old, most of the cases ranged between 51–75 years. The consistency found between studies reinforces the use of our public healthcare databases in retrospective studies.

Our study has some limitations. Population-based studies using health databases reflect the actual care of the entire population. However, there may be some limitations like codification errors. Trained personnel codify MBDS with almost no errors. Previously evaluated positive predictive value of those databases' diagnostic codes was 92.7% (95% CI: 89.1–95.4) for HZ and 93% (95% CI: 87%–96%) for intussusception.[6,20] Case definition was based on physician consultation and hospital records, and thus data on undiagnosed or misdiagnosed cases of HZ and PHN were unavailable. To minimize missing cases, we used also data from the drug prescription and dispensation databases.

Previous studies from different European countries have consistently reported percentages from 5 to 15% of HZ cases developing PHN.[21–24] In agreement with these studies, PHN incidence and duration showed in this study increased sharply with age. Given the general ageing of the population it might be expected that HZ and PHN incidence rates increase with years. Previously, a yearly increase in number of HZ cases has been reported,[21] which is also somewhat reflected in our study although without statistical significance.

Regarding comorbidities, a recent prospective study from UK which complements our work established severe immunosuppression as a strong risk factor for PHN.[9] We have excluded immunocompromised population because the only licensed vaccine is contraindicated for people with immunosuppressive conditions as is a live attenuated vaccine. So, as a known risk group for developing HZ and PHN without possibility to be immunized with this vaccine, we excluded it from the study population. Regardless methodological differences, both studies proposed COPD and diabetes among other as significant risk factors for PHN. In the present work HF was also associated with PHN with 42% increased risk.

The maintenance of health in elderly population constitutes a priority. One of the measures to reach this objective might be to

avoid infectious diseases such as HZ and its complication, PHN, which contribute to chronic diseases exacerbations and might render the affected individual dependent on their families or the healthcare system. Female gender, in addition to age and comorbidities, has also been demonstrated to be a risk factor for HZ.[6,25,26] However, pathophysiological causes of these gender differences are unknown. Also in the present study, women were more likely to develop PHN than men, coinciding with data from UK[9] and Italy, where 65% of cases of PHN3 in primary care were documented in female patients.[22] It has been hypothesized that females might have a different response to latent viral infections, which is strongly supported by the gender difference also reported in the incidence of herpes simplex.[25] However, further research is needed to elucidate the difference in the immune response between genders.

Regarding our data, around 32% of population aged from 50 to 90 years old will develop HZ, and 7% of the same population will suffer PHN. This is based on a cumulative risk calculated from 50 years old because data for younger ages were not available. This might be the reason of differences of lifetime prevalence of HZ found in previous publications, of around 50% by the age of 80.[27,28]

In 2006, the Advisory Committee on Immunization Practices recommended the zoster vaccine against HZ for adults aged ≥60 years for routine vaccination to prevent herpes zoster and its complications.[12] The Shingles Prevention Study (SPS) demonstrated that the use of the zoster vaccine reduced the burden of HZ by 61.1%, and the incidence of PHN by 66.5%.[11] Recently it has been demonstrated using Medicare data that HZ vaccine effectiveness was higher and better preserved over time for PHN and HZ-associated hospitalizations than for community HZ.[13] In view of the foregoing, our results have importance for vaccine policy for the prevention of HZ and subsequent PHN. Estimation of PHN burden and identification of risk groups constitutes a first step, but cost-effectiveness studies are needed to determine the value in vaccinating these groups of patients with the available HZ vaccine or with the new subunit zoster vaccine which will shortly be licensed.

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Author contributions

JDD is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

CMQ contributed to study conception and design; data acquisition, analysis, and interpretation; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. CMQ takes responsibility for the integrity of the data and the accuracy of the data analysis and serves as principal author.

MLL contributed to data acquisition, data cleaning, analysis and interpretation; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

JDD and AOS contributed to study design; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Role of the sponsors

The company (SPMSD) had no role in the analysis or discussion of the results.

Study design

Dr. Cintia Muñoz-Quiles confirms that the study objectives and procedures are honestly disclosed. Moreover, she has reviewed study execution data and confirms that procedures were followed to an extent that convinces all authors that the results are valid and generalizable to a population similar to that enrolled in this study.

Conflict of interest

JDD and his institution received research grants from SPMSD related to HZ vaccine. He also acted as advisor for these vaccines to GSK and SPMSD. CMQ and AOS have attended to several congresses whose registration, travel and accommodation costs have been covered by SPMSD. MLL has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.04.004.

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