Impacto y riesgo de Herpes Zóster en sujetos inmunodeprimidos en la Comunidad Valenciana

AIV_HZ_2017_04_IHZIS_JDD

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RESUMEN

Introducción

El herpes zóster (HZ) es una enfermedad causada por la reactivación del virus varicela-zóster en situaciones de disminución de la inmunidad celular. La edad avanzada y los estados de inmunosupresión favorecen el aumento de la incidencia.

En España, HZ no ha sido una enfermedad de declaración obligatoria hasta el año 2014, por lo que los datos epidemiológicos de los que se dispone son escasos. Un reciente estudio evidenció que la incidencia de HZ en la Comunidad Valenciana fue de 4.60/1000 personas-año para todas las edades (IC 95%: 4.57-4.63) durante el periodo 2007-2010.

Entre los pacientes con mayor riesgo de sufrir un HZ se encuentran los pacientes con inmunosupresión de distinto origen y grado (trastornos por inmunodeficiencia o enfermedad autoinmune, HIV, pre-trasplante, quimioterapia programada). Estos sujetos quedarían fuera del alcance de la única vacuna que existe actualmente en el mercado, por tratarse de una vacuna con virus vivos atenuados (Zostavax, Merk).

Una alternativa a este tipo de vacunas la constituye la vacuna inactivada de subunidades (glicoproteína E) obtenida por recombinación génica y con el adyuvante $AS01_B$ que se encuentra en avanzado estado de investigación y que ha dado buenos niveles de seguridad e inmunogenicidad tanto en adultos sanos como en inmunodeprimidos. La realización de un estudio poblacional que evalúe la incidencia de HZ en todos los pacientes inmunodeprimidos de diferentes tipos y grados constituye un paso previo necesario para poder evaluar el posible impacto que dicha vacuna podría tener en dicha población.

Objetivos

Primarios

Estimar la incidencia de HZ en sujetos inmunodeprimidos ≥ 18 años en la Comunidad Valenciana, entre 2009 y 2014, tanto globalmente como estratificando por grupos de edad, sexo y tipo de inmunodeficiencia (VIH, neoplasias, trasplante de órganos y trastornos por inmunodeficiencia o enfermedades autoinmunes).

Secundarios

- Estimar el riesgo de HZ en sujetos inmunocomprometidos en comparación con sujetos inmunocompetentes y comparar el consumo de recursos sanitarios relacionados con el HZ en ambos grupos (medido en términos de consultas a atención primaria debidas a HZ, hospitalizaciones y duración de las hospitalizaciones por HZ, medicación para HZ y periodos de baja laboral debidos a HZ). Estudiar también el consumo de recursos sanitarios por tipo de inmunodeficiencia.
- Estudiar el impacto del HZ sobre la patología de base (inmunodepresión) (medido en términos de número de visitas a atención primaria, hospitalizaciones y duración de las hospitalizaciones), comparando los seis meses previos al primer diagnóstico de HZ con los seis meses posteriores a dicho diagnóstico.
- Estudiar el riesgo de complicaciones del HZ en sujetos inmunocomprometidos respecto a inmunocompetentes, en global y estratificando por grupos de edad, sexo y tipo de complicación, y describir el consumo de recursos y los costes asociados.
- Estudiar el riesgo de HZ y el consumo de recursos en pacientes inmunocomprometidos en comorbilidad con diabetes y/o enfermedad pulmonar obstructiva crónica (EPOC) y/o insuficiencia cardiaca (IC) y/o enfermedad renal crónica, en comparación con sujetos inmunocompetentes.
- Estimar el riesgo de sufrir un HZ recurrente en sujetos inmunocomprometidos e inmunocompetentes.
- Estimar la prevalencia de condiciones inmunosupresoras en la población en general, globalmente y estratificando por grupos de edad, sexo y tipo de inmunosupresión.

Métodos

Tipo de estudio

Se realizará un estudio poblacional, retrospectivo de cohortes sobre el impacto y riesgo de HZ en sujetos inmunodeprimidos basado en bases de datos sanitarias (BBDD) de la Comunidad Valenciana.

Población y periodo de estudio.

Para el desarrollo del estudio se considerará a todos los sujetos residentes en la Comunidad Valenciana cubiertos por el sistema público de salud (98.3%) mayores de 18 años en el periodo comprendido entre el 1 de enero de 2007 y el 31 de diciembre de 2014.

Selección de casos

Casos de HZ: Los casos de HZ serán identificados a través de una búsqueda sistemática de todos los códigos CIE-9-MC 053.0 – 053.9: HZ y complicaciones relacionadas con HZ, tanto en SIA como en CMBD (en cualquier posición diagnóstica) durante el periodo de estudio. Se tendrán en cuenta también las posibles recurrencias.

Casos de inmunosupresión: Para la identificación de sujetos inmunocomprometidos se hará una búsqueda sistemática en SIA y en CMBD de todos los códigos CIE-9 relacionados con condiciones de inmunodepresión (ver anexo I). Los sujetos serán considerados como inmunocpmprometidos desde la fecha de aparición del código diagnóstico hasta el final del periodo de seguimiento.
Sujetos inmunocompetentes:

Variables explicativas

Como covariables para el análisis se considerarán la edad, el sexo, el año, el mes, el municipio de residencia, departamento de salud, exclusión social, nacionalidad, comorbilidad (diabetes, EPOC, IC y enfermedad renal crónica).

Análisis estadístico

Se realizará un análisis descriptivo exploratorio describiendo las variables mencionadas anteriormente mediante frecuencias, proporciones, medias, desviaciones típicas y cuantiles dependiendo del tipo de variable del que se trate, y un test chi-cuadrado como paso preliminar para explorar la asociación entre tener un HZ y las variables cualitativas consideradas.

Se estimarán las tasas de incidencia e incidencias acumuladas del primer evento registrado en la base de datos de HZ y de los casos de HZ recurrentes por sexo, grupos de edad: 18 - 29, 30 - 39, 40 - 49, 50 - 59, 60 - 69, 70 - 79 y ≥ 80 años (y en global) y por hospitalización y se calcularán sus respectivos intervalos de confianza al 95% utilizando el método exacto de Poisson.

Para evaluar el impacto del HZ sobre la inmunosupresión seleccionaremos aquellos sujetos inmunodeprimidos que a su vez tengan un diagnóstico de HZ durante nuestro periodo de estudio. En estos sujetos se compararán el número de consultas médicas y de hospitalizaciones en el periodo de 6 meses anterior al HZ respecto al periodo de 6 meses posterior al HZ.

El riesgo de HZ, HZ recurrente y HZ con complicaciones en sujetos inmunocomprometidos respecto a inmunocompetentes se estimará mediante un modelo bayesiano de regresión de Poisson ajustado por edad, sexo, año de calendario y otras comorbilidades (diabetes, EPOC, IC y enfermedad renal crónica) como términos lineales y el departamento de salud y la variable grupo (correspondientes con registros de las bases de datos) como efectos aleatorios.

La prevalencia de condiciones inmunosupresoras se estimará dividiendo el número total de pacientes inmunocomprometidos por el número total de sujetos de la población durante el periodo de estudio.

Consideraciones éticas y legales

El estudio se llevará a cabo de acuerdo con toda la legislación reguladora aplicable, incluyendo todos los requerimientos aplicables de privacidad de los sujetos, la Guía de los Principios de la Declaración de Helsinki, y las Consideraciones Éticas para Estudios Epidemiológicos.

El protocolo será remitido para su aprobación al Comité Ético de Investigación Clínica de la Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública (CEIC DGSP/CSISP).

Para el manejo de datos personales se considerará The Council for International Organizations of Medical Sciences (CIOMS), 2009, la Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal y el Procedimiento Normalizado de Trabajo del Área de Investigación en Vacunas del CSISP vigente, PNT_AIV_05, Custodia y Tratamiento de Datos de Carácter Personal.

Se llevará a cabo una disociación entre los datos de cada sujeto y los datos personales en las fuentes originales: los gestores de las bases de datos llevarán a cabo una transformación reversible del número de identificación único y almacenarán la semilla para cada individuo.

Además, el estudio será comunicado a la Agencia Española del Medicamento y Productos Sanitarios (AEMPS) para solicitar la clasificación como Estudio observacional no pos autorización (NO-EPA).

STUDY PROTOCOL (Version 1)

Impact and risk of Herpes Zoster in immunosuppressed subjects in Valencia Region, Spain

AIV_HZ_2017_04_IHZIS_JDD

Draft 1, 20 January 2017

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DEFINITIONS

Chronic kidney disease case: subjects with ICD-9-CM diagnostic codes 250.4X, 274.1X, 283.11, 403.X1, 404.X2, 404.X3, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1X, and 646.2X in SIA or CMBD.

Chronic obstructive pulmonary disease case: subjects with an ICD-9-CM code for COPD,491.XX, 492.X and 496, in SIA or CMBD in any diagnostic position, and severe cases of COPD will be considered if there is also inhaled corticosteroids prescription (COPD-ICS).

CMBD (Minimum basic data set): Spanish hospital discharge database that collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases.

Diabetes case: subjects with an ICD-9-CM code for diabetes (all ICD-9-CM 250.XX codes) in SIA or CMBD in any diagnostic position and/or with a prescription or dispensation for specific medication for diabetes in GAIA (insulin and/or oral anti-diabetic drugs).

Health Department: each of the 24 health departments of the regional health system. Each of them includes at least 1 hospital (28 hospitals in total), 1 specialty centre, and a variable number of ambulatory care centres.

Heart Failure case: subjects with an ICD-9-CM code for HF (428.X) in SIA or CMBD.

HZ complication will be defined by hospital discharge CIE-9 codes (CMBD) as follows:
053.0 Herpes zoster with meningitis
053.1 With other nervous system complications
053.10 Herpes zoster with unspecified nervous system complication
053.11 Geniculate herpes zoster
053.12 Post-herpetic trigeminal neuralgia
053.13 Post-herpetic polyneuropathy
053.14 Herpes zoster myelitis
053.19 Other central nervous system complications
053.2 With ophthalmic complications
053.20 Herpes zoster dermatitis of eyelid
053.21 Herpes zoster keratoconjunctivitis
053.22 Herpes zoster iridocyclitis
053.29 Herpes zoster with other ocular complications
053.7 With other specified complications
053.71 Otitis externa due to herpes zoster
053.79 Other specific herpes zoster complications
053.8 With unspecified complication

Immunosuppressed case: subjects with the appearance of an ICD-9-CM code related to an immunosuppressed state (see appendix 1) either in SIA or CMBD.

Incident HZ case: an incident case of HZ will be considered the first appearance of a HZ-related ICD-9-CM code in either SIA or CMBD (in any position).

Medical encounter: any recorded outpatient medical contact or visit, or hospital admission will be considered as a medical encounter.

Recurrent HZ case: a HZ case will be considered recurrent when an ICD-9 code for HZ appeared after 6 months from a previous HZ encounter.

Rural areas: Rural residence will be classified based on the law for sustainable development of the rural environment from the Regional Government. Rural areas are classified according to population density (less than 100 inhabitants per Km2), urban nucleus proximity, population trend, percentage of employment in primary, secondary and tertiary sectors and territorial structure (Available at: https://www.boe.es/boe/dias/2010/06/11/pdfs/BOE-A-2010-9237.pdf).

SIA-GAIA (Ambulatory information System - Care provision management): is a primary care database used across the entire Valencia healthcare system. This database contains primary care diagnoses (physician coded using the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM)) and all drug prescriptions (using Anatomical Therapeutic Chemical (ATC) Classification System).

SIP (Personal information system): is a regional population-based administrative database that collects and updates identification data, geographic location, assignment of health services, and access to public health services for both residents of the Valencia Community and non-residents with access to public health services.

Social exclusion risk: will be obtained from electronic database (SIP) and its classification is based on multiple aspects as unemployment, foreigner in irregular situation or without resources.

1. INTRODUCTION

1.1. Background

Herpes Zoster (HZ) is a severe disease resulting from the reactivation of Varicella Zoster Virus (VZV), which remains latent in sensory nerve ganglia after primary infection (Varicella) [1]. This reactivation seems to be a result of a waning of VZV- specific cell-mediated immunity [2] as occurs with ageing or in subjects with immunosuppressive disorders. HZ can result in dermatomal chronic pain which is its most common complication (post-herpetic neuralgia, PHN) [3]. Many patients with PHN go on to develop severe physical, occupational and societal disabilities as a consequence of the enduring pain. Both, HZ and PHN result in reduced quality of life as well as individual and societal health care costs [4].

Incidence of HZ increases strongly with age, being higher after age 50 years and affecting up to 50% of people who live to 85 years[5, 6]. Beyond age, having underlying diseases seems to increase the risk, severity and impact of zoster episodes[7, 8]. Subjects with immunosuppressive conditions due to diseases or treatments that alter the immune function (Immunodeficiency disorders and autoimmune diseases, HIV, neoplasm, organ transplantation) are among the highest risk of developing HZ [9]. In a large matched case-control study [7], a range of conditions were associated with increased risk of zoster, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, type 1 diabetes, and depression. The relative effects of many of these risk factors were larger among younger patients compared to the general population.

A live-attenuated vaccine for the prevention of herpes zoster (Zostavax, Merk, Sanofi Pasteur) was approved in 2006 and has been licensed in many countries for adults older than 50 years of age [10]. However, it is not safe to vaccinate immunocompromised individuals with live attenuated vaccines so, this vaccine is contraindicated for individuals treated with systemic immunosuppressive therapies or suffering from certain immunosuppressive diseases, limiting substantially the HZ prevention options in this patient population.

GlaxoSmithKline (GSK) is currently developing an adjuvanted recombinant VZV gE subunit vaccine (50 µg recombinant VZV gE/AS01B), which is in an advanced research stage [11] and has shown acceptable levels of safety, immunogenicity and efficacy for both, healthy and immunosuppressed (IS) adults.

Currently, there is no recommendation for HZ vaccination in Spain. Large and adequately powered studies investigating the association of underlying conditions with impact of zoster would allow the health authorities to identify the main risk groups for HZ immunization. Moreover, HZ is not currently a reportable disease in our country, and there are limited epidemiological data available. A previous study indicated an HZ incidence rate in the Valencia Region of 4.60/1000 persons-year for all ages (CI 95%: 4.57-4.63) during the period 2007-2010 [6].

A population-based study to evaluate incidence of HZ and its impact on subjects with different immunosuppressive conditions in our region constitute a previous step to make an estimation of future impact of the vaccine in this population.

1.2. Objectives

Primary objectives

To estimate the incidence of HZ in IS subjects 18 years and older in Valencia Region, from 2009 to 2014, both globally and stratified by age groups, sex and immunodeficiency type (HIV, malignancies, organ transplantation, immunodeficiency disorders and autoimmune diseases) (see table in appendix I).

Secondary objectives

- To estimate the risk of HZ in IS subjects respect to IC and to compare the health-care resource consumption related to HZ between both groups (measured in terms of outpatient visits due to HZ, hospitalizations, length of hospitalizations, medication for HZ and periods off work due to HZ). To describe the health-care resource consumption by type of immunodeficiency.
- To assess the impact of HZ on the underlying pathology (immunosuppression) (measured in terms of number of outpatient visits, hospitalizations and duration of hospitalizations), comparing the six months period before the first HZ diagnosis with the six months period after the first HZ diagnosis.
- To assess the risk of HZ complications in IS subjects respect to IC in hospitalizations, overall and stratified by age group, gender and type of complication, and to describe the healthcare resource utilization and costs associated.
- To assess the risk of HZ in IS patients in co-morbidity with diabetes and/or COPD and/or heart failure and/or Chronic Kidney Disease (CKD) comparing with IC and the resources consumption caused by HZ (outpatient visits due to HZ, hospitalizations, length of hospitalizations, medication for HZ and periods off work due to HZ).
- To estimate the risk of HZ recurrence in IS subjects and IC.
- To estimate the prevalence of immunosuppressive conditions in the general population, overall and stratified by age group, gender and immunodeficiency type.

2. DATA SOURCES

2.1. Database description

The regional health system is divided into 24 health departments. Each of them includes at least 1 hospital (28 hospitals in total), 1 specialty centre, and a variable number of ambulatory care centres. All primary care visits and hospitalizations are recorded in clinical databases. Data sources for the study will be:

Population-based administrative database

The regional population-based administrative database, SIP (Personal Information System), collects and updates identification data, geographic location, assignment of health services, and access to public health services for

both residents of the Valencia Community and non-residents with access to public health services. It includes APSIG characteristic which is an identification code defined for each person at any time including: inhabitant's registration status, nationality (Spanish or not), sex, year of birth, health department assigned, health care insurance, residence status, migrations, work activity, geopolitical group, and social exclusion. Since 2005, SIP can be linked with the hospital discharge database. All other healthcare databases are able to capture the demographic data from SIP.

Primary Care Database

Abucasis SIA-GAIA (Ambulatory Information System - Care provision management) is a primary care database used across the entire Valencia healthcare system. It was set up in 2006 and the percentage of the population included increased from 73.1% in 2007 to 88.8% in 2008 and to 95.7% in 2009. This database contains primary care diagnoses (physician coded using the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM)) and all drug prescriptions (using Anatomical Therapeutic Chemical (ATC) Classification System). In addition, the physician or paediatrician and nurse responsible recorded text about each episode and about the patient is included. The database is also used at Specialty Centres and is considered reliable since 2007.

Hospital Discharge Database

The Spanish hospital discharge database, CMBD (Conjunto Mínimo Básico de Datos), collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases. Using CMBD is compulsory for all public hospitals, and over 95% of all discharges are included. According to the Spanish Ministry of Health, data are considered reliable since 2002.

Data from these databases can be linked through a unique personal identification number, SIP (Sistema de Información Personal) [6].

2.2. Legal considerations on data management

The study and the data requests will be informed and permissions will be required to the Pharmacy Agency of the Valencian Government according to the existing legislation [Resolución de 16 de junio de 2009, de la Conselleria de Sanitat]. In order to maintain anonymization of the data, personal data in the original datasets will be dissociated: the database's managers will perform a reversible transformation of the unique identification number and they will store the seed for each individual. Analyses of the anonymised data will be carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (BUGS "Bayesian Inference Using Gibbs Sampling").

3. STUDY DESIGN

A population based, retrospective cohort study to analyse the impact and risk of HZ on IS subjects will be performed using the Valencia region's health care databases.

3.1. Study population

The Valencia region of Spain had a population of 4,980,689 inhabitants in 2015. The population of interest will be all subjects living in Valencia Region, covered by Public Health System (PHS) (over 98%)[6] and older than 18 years from 1st January 2009 to 31st December 2014. The inclusion and exclusion criteria will be the following:

Inclusion criteria:

- Subjects aged 18 years and above covered by Valencian PHS during study period.
- Subjects residing in Valencia Region.

Exclusion criteria:

- Subjects with less than 12 months of observation time at the time of inclusion in the study.
- Subjects with missing information on birth date, gender and health department.

Follow-up period:

Date of inclusion in the study will be defined as 1st January 2009 if the subject was continuously registered in PHS for at least 12 months before this date and was aged 18 years or older, or first date after 1st January 2009 when the subject was continuously registered for at least 12 months before this date and was 18 years old.

Date of end of follow-up will be defined as end of the study period (31st December 2014) or the date of exit in SIP (including death), whichever comes sooner.

3.2. Immunosuppressed cohort

For the identification of IS subjects we will search SIA and CMBD for any subject with the appearance of an ICD-9-CM code related to an IS condition (HIV, malignancies, organ transplantation, immunodeficiency disorders and autoimmune diseases) (see appendix I). Subjects will be considered as immunosuppressed from that date (first code appearance) until the end of the follow-up period.

3.3. Immunocompetent cohort

IC subjects will be considered when no codes related to an IS condition are detected in databases during the study period. The start of follow-up for the IC cohort will be the date of inclusion in the study.

The IC status of an individual may change during the study period if an ICD code for an immunosuppressive condition appears in hospitalization (CMBD) or outpatient (SIA) databases. In case of outpatient or inpatient IS diagnoses, the beginning of IS status is defined as the date in which IS disease is diagnosed and the subject is considered IS from this date until the end of the follow up period (end of the study period or exit from SIP including death).

3.4. Definition of primary outcomes

Incident and recurrent HZ

An incident case of HZ will be considered the first appearance of a HZ-related ICD-9-CM code (053.xx), in either SIA or CMBD (in any position). Any outpatient medical contact or visit, or hospital admission related to HZ will be considered as a medical encounter. Recurrence of HZ will be examined in all HZ incident cases. A recurrent HZ case will be considered when an ICD-9 code for HZ appears after 6 months from a previous HZ encounter [6]. The databases and codes utilization for HZ cases definitions have an elevated positive predictive value (92.7%; 95% CI 89.1-95.4) [6].

3.5. Definition of secondary outcomes

Health care resources consumption due to HZ

Health care resources consumption due to HZ in the six months following HZ diagnosis will be measured and compared between IS and IC subjects. This consumption will be measured in terms of number of outpatient visits, number of hospitalizations, length of hospitalizations, medication for HZ and periods off work due to HZ.

Outpatient visits

To describe the frequency of outpatient visits, each outpatient visit with an HZ diagnosis (physician coded) in the 6 months following the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

Hospitalizations

To describe the frequency of hospitalization, each hospitalization with a main or secondary HZ discharge diagnosis in the six months following the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

Length of hospitalization

To describe the length of hospitalization, number of days of each hospitalization with a main or secondary HZ discharge diagnosis in the six months following the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

Medication

Medication for HZ and PHN will be measured as number of dispensations associated to a HZ diagnostic code (antivirals, opioids, antiepileptics, antidepressants and local anesthetics) in the six months following the first HZ diagnosis registration (either in outpatient or hospitalization databases) (see appendix II for ATC codes).

Periods off work

The number and length (number of days) of periods off work due to HZ (with a HZ diagnoses) in the six months following the first HZ diagnosis registration will be considered to describe frequency of leaves due to HZ.

Health care resources consumption due to IS

To measure the impact of HZ on the healthcare resources consumed due to IS, resources consumption will be measured and compared during the six months after the HZ diagnosis respect to the six months before the HZ diagnosis. This consumption will be measured in terms of number of outpatient visits, number of hospitalizations and length of hospitalizations due to IS.

Outpatient visits

To describe the frequency of outpatient visits, each outpatient visit with an IS diagnosis (physician coded) in the 6 months before and in the 6 months after the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

Hospitalizations

To describe the frequency of hospitalization, each hospitalization with a main or secondary IS discharge diagnosis in the 6 months before and in the 6 months after the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

Length of hospitalization

To describe the length of hospitalization, number of days of each hospitalization with a main or secondary IS discharge diagnosis in the 6 months after and before the first HZ diagnosis registration (either in outpatient or hospitalization databases) will be considered.

HZ complications

HZ complication will be defined by hospital discharge CIE-9 codes (CMBD) as follows:

053.0 Herpes zoster with meningitis
053.1 With other nervous system complications
053.10 Herpes zoster with unspecified nervous system complication
053.11 Geniculate herpes zoster
053.12 Postherpetic trigeminal neuralgia
053.13 Posteherpetic polyneuropathy
053.14 Herpes zoster myelitis

053.19 Other central nervous system complications
053.2 With ophthalmic complications
053.20 Herpes zoster dermatitis of eyelid
053.21 Herpes zoster keratoconjunctivitis
053.22 Herpes zoster iridocyclitis
053.29 Herpes zoster with other ocular complications
053.7 With other specified complications
053.71 Otitis externa due to herpes zoster
053.79 Other specific herpes zoster complications
053.8 With unspecified complication

Post-herpetic Neuralgia

SIA and CMBD will be searched for 053.12 and 053.13 codes. The criteria to define post-herpetic neuralgia (PHN) cases will be the following: (1) the presence of an ICD-9 code for HZ followed, within 3 months, by an ICD-9 code indicative of PHN 053.12 or 053.13, or (2) the presence of an ICD-9 code for HZ followed by a PHN medication for more than 30 days starting within 30 days after the HZ diagnosis (See appendix II), or (3) the presence of an ICD-9 code for HZ followed, within 3 months, by the appearance of an ICD-9 code for chronic pain (338.2 code)[12]. PHN incidence rates will be calculated and compared between IS and IC subjects.

Comorbidities

Patients with diabetes will be identified if a diagnostic ICD-9-CM code for diabetes (all ICD-9-CM 250 codes) is detected in SIA or CMBD in any diagnostic position and when a prescription or dispensation for specific medication for diabetes is detected in GAIA (insulin and/or oral anti-diabetic drugs). Chronic obstructive pulmonary disease patients will be identified if a diagnostic ICD-9-CM code for COPD (491, 492 and 496) is detected in SIA or CMBD in any diagnostic position, and severe cases of COPD when there is inhaled corticosteroids prescription (COPD-ICS). Heart Failure patients will be identified when diagnostic ICD-9-CM code for HF (428 – 428.9) is detected in SIA or CMBD. CKD will be identified when diagnostic codes 250.4*, 274.1*, 283.11, 403.*1, 404.*2, 404.*3, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1*, and 646.2* are detected in SIA or CMBD.

4. STATISTICAL ANALYSIS

4.1. Estimation of sample size

Currently, approximately 4,900,000 inhabitants of Valencia Region are covered by the PHS. Since the study is restricted to subjects aged 18 years and older and approximately 20% of the Spanish population is younger than

20 years (data from Statistics National Institute, INE), we might expect approx. 4 million subjects to fulfil the inclusion criteria. Internal data from a previous study from our team, using the same health databases from Valencia Region and the same ICD-9 codes showed a prevalence of IS of 11.8% in subjects ≥ 50 years old. These data correlate with a published work with a large study population of 51 million subjects and a prevalence of IS of 11.9% for subjects ≥ 50 years old [9]. According to this and the published data, the observed prevalence of IS for subjects aged 18 years and older was approx. 7% so, we will expect around 280.000 IS subjects in the present study.

Expected precision for different HZ incidence rates

Following table shows the precision for different HZ incidence rates considering the IS population, based in previous data and publications[9]. The confidence intervals were estimated using the Poisson exact method. For this estimation a follow up period of a year has been supposed for all the 280000 IS subjects.

IS population: 280000

HZ Incidence /1000 per-yr	*RSE %	Confidence Intervals 95%
10	1.89	(9.6,10.4)
11	1.8	(10.6,11.4)
12	1.73	(11.6,12.4)
13	1.66	(12.6,13.4)
14	1.6	(13.6,14.4)
15	1.54	(14.5,15.5)
16	1.49	(15.5,16.5)
17	1.45	(16.5,17.5)
18	1.41	(17.5,18.5)
19	1.37	(18.5,19.5)
20	1.34	(19.5,20.5)

*RES; Relative standard error

4.2. Explanatory variables

The following will be considered as covariables for the analysis: age, gender, calendar year, urban/rural residence, social exclusion risk, health department and co-morbidity (diabetes, COPD, heart failure and chronic kidney disease). Rural residence will be classified based on the law for sustainable development of the rural environment from the Regional Government. Rural areas are classified according to: population density (less than 100 inhabitants per Km2), urban nucleus proximity, population trend, percentage of employment in primary, secondary and tertiary sectors and territorial structure. Social exclusion risk will be obtained from electronic database (SIP) and its classification is based on multiple aspects as unemployment, foreigner in irregular situation or without resources[13]. Health department assigned for each subject will be obtained from population-based administrative database SIP.

4.3. Explanatory analysis

We will perform an exploratory descriptive analysis for IS and IC population. The variables above mentioned will be described through frequencies, proportions, means, standard deviations and quartiles depending on the variable type and a Chi-square as a preliminary step to explore the association between HZ and considered qualitative variables.

4.4. Analysis of primary objective

We will estimate HZ incidence rates and HZ recurrence rates (number of cases per 1,000 persons-year) for IS population, globally and stratified by gender, age groups: 18 - 29, 30 - 39, 40 - 49, 50 - 59, 60 - 69, 70 - 79 y ≥ 80 years, calendar year, comorbidites, type of immunosuppression, and the same estimation will be performed for hospitalization. The respective 95% confidence interval will be calculated by the exact method of Poisson.

4.5. Analysis of secondary objective

We will estimate HZ incidence rates and HZ recurrence rates (number of cases per 1,000 persons-year) for IC population, globally and stratified by gender, age groups: 18 - 29, 30 - 39, 40 - 49, 50 - 59, 60 - 69, 70 - 79 y ≥ 80, calendar year, co-morbidites, and the same estimation will be performed for hospitalization. The respective 95% confidence interval will be calculated by the exact method of Poisson.

The risk of HZ, HZ recurrence and HZ complications in immunosuppressed subjects respect to IC will be estimated by a Bayesian mixed Poisson regression adjusted by age, gender, calendar year and other co-morbidities (diabetes, EPOC, CKD and HF) as linear terms and health department and the group variable (corresponding with records from the database) as random effects (the last-one used to solve the over-dispersion problem).

To compare the health care resources consumption between both groups we will consider the number of outpatient visits, number of hospitalizations and length of hospitalizations with a HZ code, and also the number and length of periods off work due to HZ and prescriptions for HZ during the six months following HZ diagnosis. Different statistical Generalized Linear Models (GLM) will be performed to compare IS and IC populations. As a sensitivity analysis we will compare the two cohorts by a matching. Four IC subjects per control cohort will be matched to each IS subject on the year of entry, age, gender, health department and other comorbidities. To compare the HZ incidence rates between both cohorts a Cox model will be developed.

To assess the impact of the HZ on the immunosuppression and the risk of complications, we will select all the IS subjects with a follow up period of at least six months pre- and post- HZ. Health care resources consumption will be compared between both periods (number of outpatient visits and number and length of hospitalizations). Recurrent HZ episodes will be included in the analysis only when periods will not overlap. Different statistical GLM will be developed to compare the pre and post-HZ periods.

Prevalence of immunosuppressive conditions will be estimated by dividing the total number of IS patients by the total of number of subjects in the study population during the study period. It will be estimated in general population and stratified by age group, gender and immunodeficiency type.

Dummy Table 1. Demographic characteristics for population ≥ 18 years old in the Valencia Region from 2009 to 2014

Characteristics	Population(n=)	IS (n=)	HZ (n=)	DIABETES (n=)	COPD (n=)	HF (n=)	CKD (n=)
Gender N(%)							
Man							
Woman							
Age (years) N(%)							
18-29							
30-39							
40-49							
50-59							
60-69							
70-79							
≥80							
Age (mean ± sd) N(%)		-					
Calendar year N(%)							
2009							
2010							
2011							
2012							
2013							
2014							
Health Department N(%)							
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							

23	
24	
Province N(%)	
Castellón	
Valencia	
Alicante	
Nationality N(%)	
Spanish	
Other	
Rural N(%)	
Yes	
No	
Social exclusion N(%)	
Yes	
No	

Dummy Table 2. Incidence rates of HZ (per 1000 persons - per year) by age groups, gender and year in the Valencia region in 2009-2014.

	Cases	Population	Per_year	Incidente Rate per 1000	CI (95%)
AGE					
18-29					
30-39					
40-49					
50-59					
60-69					
70-79					
≥ 80					
MAN					
Age					
18-29					
30-39					
40-49					
50-59					
60-69					
70-79					
≥ 80					
WOMAN					
Age					
18-29					
30-39					
40-49					
50-59					
60-69					
70-79					
≥ 80					
CALENDAR YEAR					
2009					

2010
2011
2012
2013
2014

* Incidences table 2 will be estimated for all immunosuppressant diseases (See appendix I).

5. DATA EXTRACTION

Data privacy will be protected by using anonymised data (see 2.2. section). The following variables will be requested to the different databases for the period from 1 January 2007 to 31 January 2015 for subjects ≥18 years old:

SIP:

- Identification block including SIP number, sex, date of birth and other geographical of birth, place and date of registration.
- Regular location block that includes complete address, health map information as health department and census information among others.
- Cessation block including cessation cause and description, cessation date and date of death (when applicable).
- APSIG codes corresponding to January 2008, June 2011 and December 2014.

SIA:

Anonymized Personal Identification Number (SIP)
Birth date
Sex
Municipality of residence
Postal code
Health department
Date of CIE-9 code activation
Dates of all outpatient contacts with specified CIE-9 codes
Date of CIE-9 code deactivation
Start date of work leave with specified CIE-9 codes
End date of work leave with specified CIE-9 codes
All specialty care visits

Corresponding to CIE-9 codes related to: HZ and its complications (0.53.xx), IS [organ transplantation (V42.x, V58.44, 996.80-996.89, 33.50-33.52, 33.6, 37.51, 41.94, 50.51-50.59, 52.80-52.86, 55.61-55.69, 41.0x), HIV

(V08, 042, 079.53, 795.71), cancers (140.0-208.xx, 99.25, 99.28) and immunodeficiency disorders and autoimmune diseases (242.00-242.01, 245.2, 279.00-279.9, 288.00-288.9, 340, 357.0, 358.00-358.01, 555.0-555.9, 556.0-556.9, 710.0-710.9, 714.00-714.9, 696.x)] (see appendix I), chronic pain (238.2), COPD (491, 492 and 496), diabetes (250.xx), HF (428 – 428.9) and CKD (250.4x, 274.1x, 283.11, 403.x1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1x, and 646.2x), for the period from 1 January 2007 to 31 January 2015.

CMBD:

Anonymized Personal Identification Number (SIP)

Birth date

Sex

Municipality of residence

Postal code

Health department

Health care district

Date of hospital admission

Date of hospital discharge

Diagnoses at discharge (main and secondary diagnoses)

Procedures during the hospitalization

Discharge destination (destination on discharge)

Corresponding to CIE-9 codes related to: HZ and its complications (0.53.xx), IS [organ transplantation (V42.x, V58.44, 996.80-996.89, 33.50-33.52, 33.6, 37.51, 41.94, 50.51-50.59, 52.80-52.86, 55.61-55.69, 41.0x), HIV (V08, 042, 079.53, 795.71), cancers (140.0-208.xx, 99.25, 99.28) and immunodeficiency disorders and autoimmune diseases (242.00-242.01, 245.2, 279.00-279.9, 288.00-288.9, 340, 357.0, 358.00-358.01, 555.0-555.9, 556.0-556.9, 710.0-710.9, 714.00-714.9, 696.x)] (see appendix I), chronic pain (238.2), COPD (491, 492 and 496), diabetes (250.xx), HF (428 – 428.9) and CKD (250.4x, 274.1x, 283.11, 403.x1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1x, and 646.2x), for the period from 1 January 2007 to 31 January 2015.

We also will request to the corresponding database the information on hospital emergencies registered during the same period and for subjects with the same codes described above. Variables requested will be emergency dates, health department, hospital, CIE-9 diagnostic codes and procedures during the emergency.

GAIA:

<u>Variables related to prescriptions:</u>

Anonymized Personal Identification Number (SIP)

Active substance code

ATC code

Date of prescription

Recipe (prescription) number (anonymized)

Number of packages (cartons, containers)

Number of shapes per package (forms)

Doses per active substance per each form

Units of the dose of active substance

Dosage per form

Cadence (Daily, timely, unique…)

Dosage cadence (in hours)

Recipe status (prescription status)

Type of prescription

Commercialization price

Start date of the treatment

End date of the treatment

<u>Variables related to dispensations:</u>

Anonymized Personal Identification Number (SIP)

Recipe (prescription) number (anonymized)

Active substance code

ATC code

Number of forms per package (forms)

Dose per each form (Dose)

Units of the Dose

Dispensation date (Billing, invoicing date)

All variables for prescriptions and dispensations will be requested for the following ATC codes prescribed to the following groups of patients during the period from 1 January 2007 to 31 January 2015:

(I) Patients aged 18 years and older with a CIE-9 codes related to HZ and its complications (0.53.xx), ATC groups:

- Direct acting antivirals (J05A)
- Aciclovir 800mg (J05AB01)

- Famcyclovir 250mg (J05AB09)
- Valaciclovir 1 mg (J05AB11)
- Local anesthetics (N01B)
- Opioids (N02A)
- Antiepileptics (N03)
- Antidepressants (N06A)

(II) Patients aged 18 years and older with a CIE-9 codes related to diabetes (250.xx), ATC groups:

- Insulins y analogues (A10A)
- Blood glucose lowering drugs, excluding insulins (A10B)

(III) Patients aged 18 years and older with a CIE-9 codes related to COPD (491, 492 and 496), ATC groups:

- Drugs for obstructive airway diseases (R03)
- Inhaled glucocorticoids (R03BA)

6. LIMITATIONS

Some people resident in Valencia Region are not in the PHS database, however this is a marginal proportion (more than 98% of the residents are in the system), so this is not expected to impact our estimates significantly.

There could be some potential diagnosis of HZ or of immunosuppression outside of the region however, the risk that these cases are not captured by the system is very low as subjects that have been affiliated less than twelve months will be excluded from the study. Because we collect data from ambulatory assistance, hospitalization and drugs prescriptions and dispensations, number of missed diagnoses is expected to be negligible.

The definition of recurrent HZ case is a conservative approach which might underestimate the recurrence rates.

Information about the causes of death is not available in our databases.

IS subjects will be considered as IS until the end of the follow up period (end of the study period or date of exit from SIP including death) because intra-hospital drug dispensation data were not available so, the end of the IS status is unknown.

7. REGULATORY AND ETHICS CONSIDERATIONS

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements, the guiding principles of the Declaration of Helsinki, and Ethical Guidelines for Epidemiological Investigations.

The study will be submitted for approval to the Ethics Research Committee of the Centro Superior de Investigación en Salud Pública (CEIC DGSP/CSISP). The study will be informed to the Spanish Medicine Agency (AEMPS) in order to request its classification (as 'Estudio post-autorización otros diseños, EPA-OD') according to the existing legislation (Orden SAS/3470/2009). The study will be also informed to the Pharmacy Agency of the Valencian Government according to the existing legislation [Resolución de 16 de junio de 2009, de la Conselleria de Sanitat].

8. GOVERNANCE

Javier Díez Domingo as Principal Investigator will be responsible for supervising and final approval of: study design, protocol, statistical analysis design, Ethics Committee submission and Spanish Medicine Agency communication, data requests and quality review, analysis, organization, discussion and presentation of results and final report.

Cintia Muñoz Quiles as Study Coordinator will be responsible for the study design and protocol, coordination of statistical analysis design activities, Ethics Committee submission and Spanish Medicine Agency communication, data requests and coordination of data quality review, coordination of data analysis, and results and final report preparation.

Mónica López Lacort as Statistician will develop the statistical analysis plan design, data cleaning, data merging and tabulation, data quality review, implementation and she will collaborate in the final report preparation.

The milestones and the timeframe of the study are the following:

- IRB and AEMPS submission (months 1-2).
- Data Collection from SIP, SIA, GAIA and CMBD (months 2-14).
- Results (months 12-20).
- Final report (month 21).
- Manuscript preparation and submission (months 21-24).

9. Appendix I. CIE-9-CM codes for immunosuppressed[12, 14].

Disease or condition	CIE-9 codes for disease	Description
Organ transplantation	V42.x, V58.44, 996.80-996.89, 33.50-33.52, 33.6, 37.51, 41.94, 50.51-50.59, 52.80-52.86, 55.61-55.69 41.0x	Solid organ transplantation or aftercare or complications Bone marrow or stem cell transplant
HIV	V08	Asymptomatic human immunodeficiency virus (HIV) infection status
	042	Human immunodeficiency virus (HIV) disease
	079.53	Human immunodeficiency virus type 2 (hiv-2)
	795.71	Nonspecific serologic evidence of human immunodeficiency virus (HIV)
Cancers	140.0-208.xx 99.25, 99.28	Malignant Neoplasms Injection or infusion of cancer chemotherapeutic substance or biological response modifier as an antineoplastic agent
Immunodeficiency disorders and autoimmune diseases	242.00-242.01	Toxic diffuse goiter (Graves' disease)
	245.2	Chronic lymphocytic tiroiditis (Hashimoto's disease)
	279.00-279.9	Disorders involving the immune mechanism
	288.00-288.9	Disease of white blood cells
	340	Multiple sclerosis
	357.0	Acute infective polineuritis (Guillain Barre Syndrome)
	358.00-358.01	Myasthenia gravis
	555.0-555.9	Regional enteritis
	556.0-556.9	Ulcerative enterocolitis
	710.0-710.9	Diffuse diseases of connective tissue
	714.00-714.9	Rheumatoid artritis and other inflammatory polyarthropathies
	696.x	Psoriasis

10. Appendix II. Medication registered for HZ and PHN (ATC codes)[15].

ATC code	Drug type	Drug name
J05A	Direct acting antivirals	Aciclovir
		Famciclovir
		Valaciclovir
N02A	Opioids	Tramadol
N03	Antiepileptics	Phenytoin
		Carbamazepine
		Gabapentin
		Pregabalin
N06A	Antidepressant	Amitriptyline
		Nortriptyline
		Imipramine
		Desipramine
N01B	Local anesthetics	Capsaicin
		Lidocaine
		Lidocaine

11. REFERENCES

1. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2010;182(16):1731-1736.

2. Arvin AM. Humoral and cellular immunity to varicella-zoster virus: An overview. J Infect Dis. 2008;197:S58-S60.

3. Johnson RW, Rice ASC. Postherpetic Neuralgia. N Engl J Med. 2014;371(16):1526-1533.

4. Gater A, Uhart M, McCool R, Preaud E. The humanistic, economic and societal burden of Herpes Zoster in Europe: a critical review. BMC public health. 2015;15:1514-1514.

5. Schmader K. Herpes zoster in older adults. Clin Infect Dis. 2001;32(10):1481-1486.

6. Morant-Talamante N, Diez-Domingo J, Martinez-Ubeda S, Puig-Barbera J, Aleman-Sanchez S, Perez-Breva L. Herpes zoster surveillance using electronic databases in the Valencian Community (Spain). BMC Infect Dis. 2013;13:463.

7. Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. BMJ (Clin Res Ed.). 2014;348:g2911.

8. Esteban-Vasallo MD, Dominguez-Berjon MF, Gil-Prieto R, Astray-Mochales J, de Miguel AG. Sociodemographic characteristics and chronic medical conditions as risk factors for herpes zoster A population-based study from primary care in Madrid (Spain). Hum Vaccin Immunother. 2014;10(6):1650-1660.

9. Chen SY, Suaya JA, Li Q, Galindo CM, Misurski D, Burstin S, et al. Incidence of herpes zoster in patients with altered immune function. Infection. 2014;42(2):325-34.

10. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271-2284.

11. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang S-J, et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. New England Journal of Medicine. 2015;372(22):2087-96.

12. Guignard AP, Greenberg M, Lu C, Rosillon D, Vannappagari V. Risk of herpes zoster among diabetics: a matched cohort study in a US insurance claim database before introduction of vaccination, 1997-2006. Infection. 2014;42(4):729-35.

13. Munoz-Quiles C, Lopez-Lacort M, Ubeda-Sansano I, Aleman-Sanchez S, Perez-Vilar S, Puig-Barbera J, et al. Population-based Analysis of Bronchiolitis Epidemiology in Valencia, Spain. The Pediatric infectious disease journal. 2016;35(3):275-80.

14. Suaya JA, Chen SY, Li Q, Burstin SJ, Levin MJ. Incidence of Herpes Zoster and persistent post-zoster pain in adults with or without diabetes in the United States. Open Forum Infectious Diseases. 2014 Aug 2;1(2):ofu049; doi: 10.1093/ofid/ofu049. eCollection 2014.

15. Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: A retrospective, population-based study. Bmc Infectious Diseases. 2010;10.

12. BUDGET

PERSONNAL COSTS				
Activity	Profile of people working on the activity	TOTAL COST	First year	Second year
Principal Investigator	Senior Researcher (Part time contract 30hr/month-16 months)	19.500 €	8.531 €	10.969 €
Oversight and final approval of the study design and protocol				
Oversight and final approval of the statistical analysis design activities				
Ethics Committee submission and Spanish Medicine Agency communication				
Requests				
Oversight and final approval of data quality review				
Analysis				
Organization and presentation of results				
Discusion of results				
Preparation of the final report				
Study coordination	PhD Researcher (Part time contract 20hr/wk-12 months)	15.156 €	6.315 €	8.841 €
Study design and protocol				
Coordination of statistical analysis design activities				
Ethics Committee submission and Spanish Medicine Agency communication				
Data requests				
Coordination of data quality review				
Coordination of data analysis				
Results				
Final report preparation				
Data managment and analysis	Statistician, Junior (Part time contract 30 hr/wk-12 months)	22.733 €	9.472 €	13.261 €
Statistical analysis plan design				
Data cleaning				
Data merging and tabulation				
Data quality review				
Implementation				
Final report preparation				
TOTAL STAFF COSTS		57.389 €	24.318 €	33.071 €
OTHER FIXED COSTS				
Type				
Data extraction				
Data extraction: Abucasis SIA-GAIA		2.000 €	2.000 €	
Data extraction: CMBD		2.000 €	2.000 €	
Data extraction:SIP		2.000 €	2.000 €	
Ethical and Regulatory processes				
IRB submission and dispenses, Spanish Medicines Agency classification		2.000 €	2.000 €	
OVERHEADS 15%				
Management and admimnistrative expenses		9.808,5 €	4.847,7 €	4.960,65 €
TOTAL BUDGET		75197,4 €	37.165,7 €	38.031,7 €

TIMELINES	MONTHS																							
Activities	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Study design and protocol																									
IBR and AEMPS submission																									
Data collection SIA, GAIA, CMBD																									
Data management and analysis																									
Primary Objective																									
Secondary Objectives																									
Provisional Report Review and discusion																									
Secondary Objectives																									
Results interpretation and discusion																									
Final Report																									
Manuscript Preparation and Submission																									