Incidence of herpes zoster amongst adults varies by severity of immunosuppression

Carsten Schröder, Dirk Enders, Tania Schink, Oliver Riedel

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Corresponding author
Oliver Riedel

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Incidence of herpes zoster in adults with different severities of immunosuppression in Germany

Carsten Schröder[a]; Dirk Enders[b]; Tania Schink[a], Oliver Riedel[a]

[a] Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

[b] Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

Running title

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Corresponding author

PD Dr. rer. nat. Oliver Riedel

Leibniz Institute for Prevention Research and Epidemiology - BIPS

Achterstraße 30

28359 Bremen

Germany

E-Mail: riedel@leibniz-bips.de

Phone: +49 421 218 56883

Abstract

Objectives: We examined the incidence of herpes zoster in immunocompromised adults (≥ 18 years) with different severities of immunosuppression and assessed the prevalence of complications and of various kinds of healthcare resource utilisation.

Methods: German claims data from more than ten million adults were used to calculate annual incidence rates of herpes zoster for the years 2006-2012 and to analyse the prevalence of complications, physician visits, hospitalisations, and antiviral and analgesic treatments using a cohort design. The analyses were stratified by age, sex, and severity of immunosuppression, defined by immunocompromising conditions and drug therapies.

Results: The incidence rate per 1,000 person-years of herpes zoster was almost twice as high in immunocompromised patients (11.5 (95% confidence interval (CI): 11.4-11.6)) compared to immunocompetent subjects (5.9 (95% CI: 5.8-5.9)). The incidence rate was higher in highly immunocompromised patients (13.4 (95% CI: 13.2-13.6)) than in patients with a low severity of immunosuppression (10.0 (95% CI: 9.8-10.1)). These differences were observed for both sexes and in all age groups. Complications, outpatient physician visits, hospitalisations, and analgesic treatments occurred more frequently in immunocompromised patients as well.

Conclusions: Our results show that immunocompromised individuals are affected by the disease in particular and that the burden of herpes zoster is highest in severely immunocompromised patients.

Introduction

Infection with the varicella zoster virus (VZV) usually occurs during infancy, causing chickenpox [1]. Decades later, the latent virus can be reactivated and result in herpes zoster (HZ) which is usually characterised by a painful skin rash [2]. Since the reactivation of the VZV is typically associated with a decline in cell-mediated immunity, older and immunocompromised (IC) individuals are at higher risk of developing HZ and its complications like postherpetic neuralgia (PHN) and VZV vasculopathy [2-9]. Accordingly, a recently published systematic review reported an HZ incidence rate (IR) between 6 and 8 per 1,000 person-years (py) in 60-year-olds and between 8 and 12 per 1,000 py at age 80 [10]. Studies also observed much higher IRs in IC individuals [11-13]. Weitzman et al. [11], for example, observed an HZ IR of 12.8 per 1,000 py in IC subjects as compared to 3.5 per 1,000 py in the total population. In a large study based on German health insurance data, Hillebrand et al. [12] found an HZ IR about 75% higher in IC patients than in immunocompetent ones.

While the epidemiology of HZ is generally well understood, data on the burden in different IC populations is more limited. So far, studies assessed the HZ incidence for single IC conditions [5, 14, 15] or distinguished between the general population or immunocompetent individuals and IC patients [12, 16, 17] but there was no further differentiation between different severities of immunosuppression. Such data is essential, however, since populations with different severities of immunosuppression may require different prevention strategies. This is for example the case with regard to vaccination where the currently available attenuated vaccine cannot be used in severely IC patients.

Therefore, the aim of this study was to estimate the incidence of HZ in a representative sample of German adults with different severities of immunosuppression. Besides, we assessed the prevalence of HZ complications and different aspects of healthcare resource utilisation in these populations.

Methods

Data source

The German Pharmacoepidemiological Research Database (GePaRD), which consists of claims data from four statutory health insurances (SHIs), was used for this study. At the time of the study's inception, GePaRD contained information on demographics, outpatient prescriptions, hospitalisations, and diagnoses for the years 2004-2012 [18]. In the database, diagnoses are coded according to the International Classification of Diseases, 10th Version, German Modification (ICD-10-GM). Outpatient data include diagnoses (on a quarterly basis) with information on the diagnostic confidence (assured, suspected) and drug prescriptions. Prescription data contain the exact dates of prescription and pharmacy dispensation, information on the prescribing physician's specialty, as well as the Anatomical Therapeutic Chemical (ATC) code and the defined daily dose (DDD) of the drugs. Hospitalisation data comprise admission and discharge dates as well as admission and discharge diagnoses (including primary, secondary, and ancillary diagnoses).

Study Design

We used a cohort design to examine the annual incidences of HZ and its manifestations for the years 2006-2012. Only individuals with an age of at least 18 years in the respective study year and continuous insurance coverage during the two years preceding cohort entry (baseline period) were included in the annual cohorts. In addition, subjects were not allowed to have a diagnosis of HZ in the 12 months preceding cohort entry to ensure that only incident cases were considered. Subjects entered the annual cohorts on January 1st, or, if an HZ diagnosis was coded in the year before the respective study year, on the day exactly one year after the last HZ diagnosis. Subjects exited the annual cohorts either on the date their insurance coverage ended, or on the date of an HZ diagnosis, or at the end of the respective study year.

To estimate the prevalences of HZ-related complications, concomitant diseases, and different kinds of healthcare resource utilisation among HZ patients, another cohort was built which included all subjects from the annual cohorts with at least one HZ diagnosis identified between 2006 and 2012. Cohort entry was on the date of the first HZ diagnosis. Subjects left this cohort either when their insurance coverage ended or at the end of the study period (December 31st, 2012).

Outcomes

Herpes zoster

HZ was defined as inpatient diagnosis (primary, secondary, or ancillary) or outpatient diagnosis (coded as "assured") of an ICD-10-GM code starting with B02. Using the fourth digit, the ICD-10-GM allows to differentiate between the HZ manifestations zoster encephalitis (B02.0), zoster meningitis (B02.1), zoster with other nervous system involvement (B02.2), zoster ocular disease (B02.3), disseminated zoster (B02.7), zoster with other complications (B02.8), and zoster without complications (B02.9). Diagnoses on the day of the first HZ diagnosis were used to define the HZ manifestations.

HZ-related Complications

PHN was defined as inpatient diagnosis (primary, secondary, or ancillary) or outpatient diagnosis (coded as "assured") of the ICD-10-GM code G53.0 recorded in the quarter of the HZ diagnosis or in one of the two following quarters. The diagnosis PHN was also assumed if an HZ patient received pain medication (listed in Supplementary Table 1) during the quarter of the HZ diagnosis or during the following quarter. The ICD-10-GM codes listed in Supplementary Table 2 were used to identify cases of VZV vasculopathy. Only hospital main discharge diagnoses in the quarter of the HZ diagnosis and in the following two quarters were considered.

Concomitant diseases

Nerve palsies, lateral hemiparesis, pneumonia, hepatitis, and encephalitis, myelitis, encephalomyelitis were identified by inpatient diagnoses (primary, secondary, or ancillary) and outpatient diagnoses (coded as "assured") of the respective ICD-10-GM codes (see Supplementary Table 3) in the quarter of the HZ diagnosis and in the following quarter. Diagnoses of lateral hemiparesis, which can occur after a longer period [11], were also identified in the second quarter after the HZ diagnosis. These diseases were not labelled complications since we cannot ensure that they were actually associated with HZ.

Healthcare resource utilisation

The numbers of outpatient physician visits, hospitalisations, and prescriptions of antivirals and analgesics (listed in Supplementary Table 1) were analysed in the quarter of the HZ diagnosis and in the following two quarters. Only hospitalisations with a coded diagnosis of HZ (primary, secondary, or ancillary diagnosis) were considered. To calculate the duration of drug treatment, information on the prescribed amount and the DDD were used.

Immune status

The immune status was ascertained on the date of the first HZ diagnosis during the studied year and was based on immunocompromising (IC) conditions and medications. Patients were considered IC if they had at least one IC condition or a prescription of an IC drug. The IC conditions were: infection with human immunodeficiency virus (HIV), malignant neoplasms, chronic kidney disease, organ transplantation, stem cell transplantation, and autoimmune diseases (see Supplementary Table 4 for a comprehensive list with ICD-10-GM codes). Diagnoses were identified in inpatient (primary, secondary, and ancillary diagnoses) and outpatient data (diagnoses coded as "assured") from the first day of insurance coverage until the first HZ diagnosis. IC drugs included corticosteroids for systemic use, antineoplastic drugs, immunosuppressants, and disease-modifying antirheumatic drugs (see Supplementary Table 5). Patients were considered IC during the time of drug exposure, starting on the day

when the drug was dispensed. Information on the prescribed amount and the DDD were used to calculate the duration of drug exposure. IC patients were further categorised into "high IC" and "low IC" depending on the strength of the immunosuppressive effect of the respective condition or drug therapy as described in Table 1. Individuals not identified as IC were considered immunocompetent.

Statistical analyses

Annual IRs of HZ and its manifestations were calculated stratified by sex, 5-year age groups, immune status (immunocompetent, IC, low/high IC), and type of IC condition/therapy at the date of the first HZ diagnosis. Since immune status and type of IC condition or therapy varied over time, person-time for each subject was split into periods with different severities of immunosuppression and different IC conditions/therapies. IRs (per 1,000 py) were calculated by dividing the number of events which occurred during the respective person-time in the respective stratum by the total person-time in that stratum. 95% CIs were calculated using the substitution method [19], assuming a Poisson distribution for the number of events.

The proportions of HZ patients with HZ-related complications, concomitant diseases, outpatient physician visits, hospitalisations, and prescriptions of antivirals or analgesics were calculated stratified by sex, age group, and immune status by dividing the number of patients with the specific outcome in the specific stratum by the total number of HZ patients in that stratum.

Ethics, consent, and registration

Use of SHI data for scientific research is regulated by the Code of Social Law (SGB X) in Germany. The use of the data for this study was approved by all involved SHIs and their governing authorities. Informed consent and ethical approval were not needed.

The study was registered in the register of the European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance (ENCePP; No.: EUPAS17402).

Results

Study population

The annual study cohorts included a minimum of 9,554,821 (in 2008) and a maximum of 10,193,093 (in 2012) adult individuals with a higher share of women (55.1-56.7%). Between 2006 and 2012, the median age increased from 49 to 51 years. Table 2 shows the characteristics of the cohorts exemplarily for the first and the last study year. During the study period, the proportion of subjects in the study population categorised as IC increased from 25.5 to 34.0%.

Incidence of herpes zoster

The overall HZ IR varied between 6.76 (95% CI: 6.71-6.82) per 1,000 py in 2006 and 7.52 (95% CI: 7.47-7.58) in 2012. In IC patients, the IR varied between 11.29 (95% CI: 11.14-11.45) and 11.50 (95% CI: 11.38-11.63) per 1,000 py. The IR was between 9.51 (95% CI: 9.29-9.73) and 9.99 (95% CI: 9.83-10.14) in low IC subjects and between 12.53 (95% CI: 12.32-12.74) and 13.65 (95% CI: 13.44-13.86) in highly IC patients. In immunocompetent subjects, the IR ranged between 5.62 (95% CI: 5.56-5.67) and 5.87 (95% CI: 5.81-5.92) per 1,000 py. Similar results were observed for men and women with higher IRs among women (Figure 1).

In each study year, the HZ IR increased with age with a marked increase in patients older than 50 years. As illustrated exemplarily for 2012 in Figure 2, this was true for all immune statuses.

With reference to IC conditions in 2012, we observed the highest IR in subjects with a diagnosis of stem cell transplantation (37.19 (95% CI: 31.97-43.02) per 1,000 py) (Table 3).

Regarding subjects with IC drug treatment, the HZ IR was highest among patients with rituximab treatment (45.04 (95% CI: 31.72-62.09) per 1,000 py) followed by antineoplastic drugs (21.39 (95% CI: 19.45-23.46)), corticosteroids (20.61 (95% CI: 19.95-21.29)), and immunosuppressants (19.00 (95% CI: 17.76-20.30)). Similar patterns were observed in every study year.

HZ manifestations, complications, and concomitant diseases

Zoster without complications was the most common HZ manifestation and with the exception of the rare zoster meningitis, all manifestations occurred more frequently in patients with a higher severity of immunosuppression (Table 4).

Among the 442,979 HZ cases which we observed during the study period, 27.0% suffered from PHN (males: 24.9%, females: 28.2%), 0.7% from VZV vasculopathy, 1.5% from pneumonia, 1.2% from lateral hemiparesis, 0.8% from nerve palsies, 0.6% from hepatitis, and 0.3% from encephalitis, myelitis, or encephalomyelitis. All of these diseases occurred more frequently among IC patients (Table 5).

Healthcare resource utilisation

The median number of outpatient physician visits was 10 for IC patients and 7 for immunocompetent patients. Of the 4,056,985 observed visits, 28.5% accounted for physicians for internal and general medicine, 11.4% for general practitioners, and 6.2% for dermatologists.

During the quarter of the HZ diagnosis or during the two following quarters, 6.5% of all HZ patients were hospitalised (only considering hospitalisations with any coded HZ diagnosis). Hospitalisations occurred in 10.0% of the IC patients with a median of 1 hospitalisation per patient. Among immunocompetent HZ patients, 4.2% were hospitalised (median=1).

Antiviral drugs were prescribed for 74.0% of the IC HZ cases with a median treatment duration of 7 days. Of these patients, 62.5% received aciclovir, 38.8% brivudine, 1.5% valaciclovir, and 0.4% famciclovir. Among immunocompetent HZ patients, 74.9% received antiviral medication (median duration=7 days). Aciclovir was prescribed for 61.8%, brivudine for 39.2%, valaciclovir for 0.9%, and famciclovir for 0.2% of these patients.

Pain medication was prescribed for 31.0% of the IC HZ patients with a median treatment duration of 28 days. Among immunocompetent HZ patients, 19.6% were treated with analgesics (median duration=20 days). Tramadol was prescribed most frequently in IC and immunocompetent patients with a share of 33.7 and 34.2%, respectively.

Discussion

Our results showed an incidence of HZ about twice as high in IC than in immunocompetent subjects and higher incidences with increasing severity of immunosuppression. Besides, we observed higher incidences among women and in the older age groups. Among HZ patients, the prevalences of complications, concomitant diseases, hospitalisations, and treatments with pain medication increased with increasing severity of immunosuppression.

The higher HZ incidence among women is in accordance with studies from different countries and is thought to result from sex differences regarding care-seeking behaviour, which may influence results based on secondary data [11-13, 20-23]. Different immune responses to viral infections in men and women are assumed to play a role as well [22].

The higher IRs in the older age groups and the particularly steep increase in the age groups between 50 and 80 years have also been observed in other studies [10]. The rising susceptibility to HZ with age is thought to result from a decreasing cell-mediated immune response to the VZV caused by immunosenescence [24, 25].

A higher HZ incidence in IC patients has been observed previously [11-13]. Insinga et al. [13] examined the HZ IR using health insurance data of about four million individuals from all age groups in the United States. For the years 2000/2001, they found an IR of 10.3 (95% CI: 9.7-11.0) per 1,000 py for IC patients and of 3.0 (95% CI: 2.9-3.0) for immunocompetent subjects. In the Israeli study by Weitzman et al. [11], the HZ IR was 12.2 per 1,000 py in IC individuals (aged ≥25 years) as compared to 3.5 among all study subjects (also including persons aged <25 years). Between 2005 and 2009, Hillebrand et al. [12], who also used GePaRD data, found an HZ IR almost twice as high in IC than in immunocompetent subjects (11.8-14.3 vs. 6.1-7.2 per 1,000 py). These results are very much in accordance with our findings, although the share of IC individuals in our study population was much higher (25.5-34.0 vs. 9%). This can be explained by the fact that Hillebrand et al. included individuals younger than 18 years, where the prevalence of immunosuppression is presumably lower than in the adult population. Moreover, they used a narrower spectrum of IC conditions (HIV, malignant neoplasms, immunodeficiency, transplanted organ/tissue status), did not consider IC medications, and only used a period of 12 months to identify IC conditions, whereas this period was at least twice as long in our study. How we defined the immune status also contributed to the high proportion of IC subjects in our study, especially in the later study years. Once a diagnosis of a chronic IC condition was made, the patient remained IC until the end of the follow-up period.

Our results showed an HZ IR about 40% higher in patients with a high severity of immunosuppression than in those with a low severity. Since our study was the first to investigate these differences between different severities of immunosuppression, comparisons with other studies are not possible. However, the observed trend of an increasing HZ incidence with a decreasing immune status dovetails with studies examining HZ in patients with different IC conditions. They report, for example, increased risks of developing HZ for patients suffering from inflammatory bowel disease [26], peptic ulcer [27], systemic lupus

erythematosus [28], or chronic kidney disease [16], and highly increased risks for patients with HIV [15, 16, 29], malignant neoplasms [5, 16, 30, 31], or organ transplantation [32, 33].

The prevalences of PHN, VZV vasculopathy, all selected concomitant diseases, hospitalisations, and treatments with analgesics were lowest in immunocompetent and highest in highly IC HZ patients. Higher prevalences of HZ-related complications and higher rates of healthcare utilisation in IC patients have also been observed in other studies [11, 12, 34]. These findings indicate that a lower immune status is associated with a higher risk of a more complicated disease course and potentially with a higher rate of long-term effects. Beyond that, the results show that the immune status does not only affect the personal but also the socioeconomic burden of HZ.

The size of the database used is a major strength of this study. GePaRD is representative for the German population regarding age and sex distribution, region of residence, number of hospital admissions, and drug use [35, 36]. Drug exposure was determined based on pharmacy dispensing data which is considered the gold standard in pharmacoepidemiological research, although the patients' adherence to drug prescriptions and the prescribed daily dose are not known [37]. We were not able to ensure that the prescribed analgesic drugs were actually prescribed to treat zoster pain which might have contributed to the rather high prevalence of PHN. Another limitation resides in the fact that patients who did not consult a physician for their HZ condition cannot be identified in the database. This might have led to an underestimation of the HZ incidence. But since HZ usually causes discomfort and pain, the number of patients not contacting a physician should be relatively low. Some underestimation is possible with regard to the prevalences of the HZ complications and concomitant diseases if physicians only coded the primary disease or the most severe condition. The fact that we used outpatient as well as inpatient data (including primary, secondary, and ancillary diagnoses) to identify diagnoses should have limited the risk of underestimation. However, for data protection reasons, it was not possible to validate GePaRD data by looking at physicians'

patient records.

Some misclassification with regard to the patients' immune status is possible due to the fact that outpatient diagnoses were only available related to a quarter of a year. If the immune status was only defined by an outpatient diagnosis, the middle of that quarter had to be used as an approximation of the date when the immune status changed. The left truncation of data years in GePaRD may have caused some misclassification as well. For example, patients who were diagnosed with an IC condition prior to the earliest baseline period (2004-2005) would erroneously not have been identified as IC during the study period, unless continued coding of the IC condition occurred. But since the IC conditions under study are chronic diseases, continued coding should usually have occurred. Besides immunosuppressive drugs, we used a wide range of IC conditions to identify IC individuals. However, defining the patients' severity of immunosuppression was difficult since we relied exclusively on ICD-10 diagnoses with no additional information like laboratory parameters. Therefore, it was not possible to consider different disease severities. Hence, some highly IC patients might have been counted as low IC and vice versa.

Conclusions

We were able to examine, for the first time in Germany, the burden of HZ in adults with different severities of immunosuppression. With decreasing immune status, we observed higher incidences of HZ and higher prevalences of complications and healthcare resource utilisations. This indicates that IC patients are particularly affected by the disease and that the burden is highest in severely IC patients. Our findings make it possible to estimate the number of people with different severities of immunosuppression who are affected by HZ. This can be useful when planning new prevention strategies (for instance a vaccination which can be used in severely IC patients).

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Conflict of Interest

C.S., D.E., T.S., and O.R. are working in departments that occasionally perform studies for pharmaceutical companies. These companies include Bayer, Celgene, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA.

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Tables

Table 1. Definition of immune status based on immunocompromising conditions and immunosuppressive drug therapies[a]

IC condition / drug	Immune status
HIV	"High IC" from diagnosis until end of study period
Malignant neoplasms	"High IC" until two years after diagnosis; after that "low IC" until end of study period
Chronic kidney disease	"High IC" from diagnosis until end of study period
Organ transplantation	"High IC" from diagnosis until end of study period
Stem cell transplantation	"High IC" until two years after diagnosis; after that "low IC" until end of study period
Autoimmune diseases[b]	"Low IC" from diagnosis until end of study period
Antineoplastic drugs Immunosuppressants Disease-modifying antirheumatic drugs Corticosteroids for systemic use	"Low IC" during time of treatment
High-dose glucocorticoids: Betamethasone (≥ 2,7 mg/day) Dexamethasone (≥ 3,2 mg/day) Fluocortolone (≥ 20 mg/day) Methylprednisolone (≥ 16 mg/day) Paramethasone (≥ 8 mg/day) Prednisolone (≥ 20 mg/day) Prednisone (≥ 20 mg/day) Triamcinolone (≥ 16 mg/day) Hydrocortisone (≥ 80 mg/day) Cortisone (≥ 100 mg/day) Prednylidene (≥ 24 mg/day) Deflazacort (≥ 24 mg/day) Cloprednol (≥ 15 mg/day)	"High IC" during time of treatment and for three months after end of treatment if the treatment lasted for more than two weeks

[a] The choice of conditions and drug therapies as well as their IC effects were mainly based on the 2013 IDSA guideline (Rubin LG, Levin MJ, Ljungman P et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014; 58:309-318)

[b] See Supplementary Table 4 for a comprehensive list of these diseases.

Abbreviation: IC=Immunocompromising/immunocompromised

Table 2. Characteristics of the study cohorts (values are expressed as N and % unless stated otherwise)

Study year	**2006 (N=9,627,913)**	**2012 (N=10,193,093)**
Male	4,172,923 (43.3)	4,568,343 (44.8)
Female	5,454,990 (56.7)	5,624,750 (55.2)
Age (years)		
Mean (SD)	50.2 (17.4)	52.1 (17.7)
Minimum	18	18
Median	49	51
Maximum	110	111
Age groups (years):		
18-19	126,659 (1.3)	95,738 (0.9)
20-29	1,272,321 (13.2)	1,174,393 (11.5)
30-39	1,413,131 (14.7)	1,416,693 (13.9)
40-49	2,053,204 (21.3)	1,972,914 (19.4)
50-59	1,682,819 (17.4)	1,979,154 (19.4)
60-69	1,667,911 (17.3)	1,503,160 (14.8)
70-79	945,277 (9.8)	1,431,830 (14.1)
80-89	404,062 (4.2)	521,719 (5.1)
≥90	62,579 (0.6)	97,492 (1.0)

Abbreviation: SD=Standard deviation

Table 3. Incidence rates of herpes zoster in 2012 by type of immunocompromising condition

	Incidence rate per 1,000 py	**95% CI**
Stem cell transplantation	37.19	31.97-43.02
Systemic lupus erythematosus	16.49	14.35-18.85
Seropositive rheumatoid arthritis	16.23	15.35-17.15
Lupus erythematosus	16.20	14.60-17.93
Polymyalgia rheumatica	15.75	14.87-16.66
Transplanted organ status	14.48	12.66-16.50
Other rheumatoid arthritis	14.44	14.03-14.85
Chronic kidney disease	13.87	13.53-14.22
HIV	12.98	11.95-14.07
Malignant neoplasms	12.52	12.35-12.70
Ulcerative colitis	10.78	10.16-11.43
Crohn's disease	10.66	9.94-11.41
Psoriasis	10.53	10.27-10.79
Autoimmune thyroiditis	9.74	9.42-10.07
1 disease	10.39	10.25-10.52
2 diseases	13.90	13.58-14.22
≥2 diseases	18.38	17.67-19.12

Abbreviations: CI=Confidence interval; py=Person-years

Table 4. Incidence rates (per 1,000 person-years) and 95% confidence intervals of the different herpes zoster manifestations in 2012 stratified by immune status

		IC		
	Immunocompetent	**Low IC**	**High IC**	**Total**
Zoster without complications	5.04 (4.99-5.09)	8.44 (8.30-8.59)	11.04 (10.86-11.23)	9.60 (9.49-9.72)
Zoster with other nervous system involvement	0.73 (0.71-0.75)	1.48 (1.42-1.54)	2.18 (2.10-2.26)	1.79 (1.74-1.84)
Zoster ocular disease	0.31 (0.29-0.32)	0.54 (0.51-0.58)	0.78 (0.73-0.82)	0.65 (0.62-0.68)
Zoster with other complications	0.25 (0.24-0.26)	0.45 (0.42-0.48)	0.71 (0.66-0.75)	0.56 (0.54-0.59)
Disseminated zoster	0.03 (0.02-0.03)	0.06 (0.05-0.08)	0.12 (0.10-0.14)	0.09 (0.08-0.10)
Zoster encephalitis	0.02 (0.02-0.03)	0.03 (0.02-0.04)	0.07 (0.06-0.09)	0.05 (0.04-0.06)
Zoster meningitis	0.01 (0.00-0.01)	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.01 (0.01-0.01)

Abbreviation: IC=Immunocompromised

Table 5. Prevalence of herpes zoster complications and concomitant diseases among the herpes zoster cases (2006-2012) stratified by immune status (values are expressed as %)

		IC		
	Immuno-competent (N=267,451)	**Low IC (N=79,717)**	**High IC (N=95,811)**	**Total (N=175,528)**
Postherpetic neuralgia	22.5	30.5	36.6	33.8
VZV vasculopathy	0.5	0.7	1.3	1.0
Pneumonia	0.8	1.3	3.4	2.5
Lateral hemiparesis	0.8	1.1	2.5	1.9
Nerve palsies	0.6	1.0	1.1	1.1
Hepatitis	0.5	0.7	0.8	0.8
Encephalitis, myelitis, encephalomyelitis	0.2	0.4	0.5	0.4

Abbreviation: IC=Immunocompromised

Figure legends

Figure 1. Incidence rate of herpes zoster stratified by immune status in males (black, left) and in females (grey, right)

Abbreviation: IC=Immunocompromised

Figure 2. Incidence rate of herpes zoster in 2012 stratified by age group

Abbreviation: IC=Immunocompromised