Epidemiology and cost of Herpes Zoster and Postherpetic Neuralgia in Germany

Bernhard Ultsch[*1,2]; Ingrid Köster[3], Thomas Reinhold[4]; Anette Siedler[1];
Gérard Krause[5,6]; Andrea Icks[7]; Ingrid Schubert[3]; Ole Wichmann[1]

*corresponding author
[1]Immunisation Unit, Robert Koch Institute, Berlin, Germany
[2]Charité - University Medical Centre, Berlin, Germany
[3]PMV Research Group, University of Cologne, Cologne, Germany
[4]Institute for Social Medicine, Epidemiology and Health Economics, Charité - University Medical Centre, Berlin, Germany
[5]Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
[6]Department for Epidemiology, Helmholtz Centre for Infection Research, Braunschweig, Germany
[7]Institute for Biometry and Epidemiology at the German Diabetes-Center, Heinrich Heine University, Düsseldorf, Germany

Contact information of corresponding author:
Bernhard Ultsch
Immunization Unit
Department for Infectious Disease Epidemiology
Robert Koch Institute
DGZ-Ring 1
13086 Berlin
GERMANY
Phone: +49 (0)30 18 754 3314
Fax: +49 (0)30 18 754 3514
E-Mail: UltschB@rki.de

JEL codes: C81; I11; I13; I19; J14
Key words: Herpes zoster; postherpetic neuralgia; epidemiology; cost of illness; Germany

Acknowledgements

The Authors gratefully acknowledge the supporting consultancy of Dr. Andrej Rasch (Federal Joint Committee (G-BA)). Furthermore we like to thank AOK Hesse, KV Hesse, and the Ministry of Social Affairs Hesse for the permission of data access.

Potential conflicts of interest: Before initiation of this research, BU was an employee of Sanofi Pasteur MSD (provider of a herpes zoster vaccine) from April 2008 to May 2010. IK and IS conducted a research project in 2007, which was fully funded by Sanofi Pasteur MSD (provider of a herpes zoster vaccine). For all other authors: No competing interests. Funding for this study was fully provided by the Robert Koch Institute (FKZ 1362/1-983).

Abstract

Background: After acquiring a varicella-virus-infection, the virus can reactivate and cause herpes zoster (HZ), a painful skin rash. A complication of HZ is long-term persistence of pain after rash has resolved (so-called postherpetic neuralgia, PHN). We aimed to describe the epidemiology of HZ/PHN and to estimate HZ/PHN-related costs in the German statutory-health-insurance (SHI) system (~85% of the total population).

Methods: Treatment data of one large SHI was utilized, containing data on approximately 240,000 insurant and their utilization of services in 2004-2009. Identification of HZ- and PHN-cases was performed based on 'International Statistical Classification of Diseases' and specific medications using a control-group design. Incidences per 1,000 person-years (PY) and costs-of-illness for one year following HZ-onset considering the payer and societal perspective were calculated. All amounts were inflated to 2010 Euros. Population-figures were standardized and extrapolated to the total SHI-population in Germany in 2010.

Results: A mean annual incidence of 5.79 HZ-cases per 1,000 PY was observed, translating into an estimated 403,625 HZ-cases per year in the total SHI-population. Approximately 5% of HZ-cases developed PHN. One HZ-case caused on average € 210 and € 376 of costs from the payer and societal perspective, respectively. The development of PHN generated additional costs of € 1,123 (€ 1,645 societal perspective). Total annual HZ/PHN-related costs were estimated at € 182 Million (€ 105 Million) to the society (payer).

Conclusion: HZ and PHN place a considerable burden on the German SHI-system. Since HZ-vaccines will be available, a health-economic evaluation of these vaccines should be conducted.

Introduction

Before the introduction of routine childhood vaccination against chickenpox (varicella), the lifetime risk of acquiring a varicella-zoster virus (VZV) infection was almost 100% [1]. After recovery from varicella, which affects mainly children, the virus remains latent in the dorsal root ganglia of the infected person [2]. Due to decreasing VZV-specific T-cell-immunity with increasing age, a reactivation of the virus can occur and manifests as shingles (herpes zoster, HZ) [3,4]. But also other causes (e.g. HIV or psychological stress) can contribute to the reactivation of the virus [5]. HZ is a self-limiting and painful rash that usually affects the skin of the trunk or the head for approximately four weeks [6-8]. About 20 to 30% of individuals develop HZ at least once in their lifetime [9]. The main complication of HZ is postherpetic neuralgia (PHN), a long-lasting burning and severe pain persisting for months in the affected skin area after the rash has resolved [10,11].

In 2006 the European medicine agency (EMA) licensed the first vaccine against HZ and PHN for people 50 years of age and older [12]. This live-attenuated vaccine demonstrated its efficacy in a randomized controlled trial including individuals aged ≥60 years, reducing HZ and PHN-incidence by 51% and 67%, respectively [13]. The vaccine's effectiveness was confirmed in a community setting in the US among adults aged 60 years or older [14]. A recent clinical trial determined a vaccine efficacy in preventing HZ in people aged 50-59 years by almost 70% [15]. Another vaccine candidate is currently tested in a phase III clinical trial for its efficacy in preventing HZ in the elderly [16]. As of 2012, the licensed vaccine was not yet available on the market in most European countries. But it can be expected, that the vaccine will be available on the German market in the near future.

In order to support the evidence-based decision-making process concerning a potential HZ-vaccination recommendation in Germany, we aimed to describe the epidemiology and to estimate the cost of HZ and PHN in the German statutory health insurance (SHI) system.

Methods

The data-base

In Germany, almost 85% of the population (69.6 Million people (February 2012 [17]) is covered by the statutory health insurance (SHI). As of October 2012, there were in total 144 SHIs in Germany that offered equal mandatory services to their members. The data-base used in this retrospective analysis contained a sample of the SHI 'Allgemeine Ortskrankenkasse' (AOK) Hesse (which is one of the 16 federal states in Germany) and data from the Regional Association of SHI-Accredited Physicians (KV) of Hesse [18]. Therefore, this data-base combines both, patient-related billing-data from the SHI and patient-related treatment-documentation from the KV. The combined data-base covers a population of approximately 240,000 individuals, for which information on age, sex, and information concerning the insurance status (e.g. employed, retired, etc.) were included. The following information on services is recorded on a patient-level in the data-base: treatment details in medical practices (where the outpatient care is organized in Germany), drug prescriptions, diagnoses

records, and therapeutic appliance, inpatient treatment, sick-pay, co-payment, and sick-leave. Since the data-base included all institutions of the healthcare system in Germany, hospital admissions, hospital discharge, and referrals between general practitioners (GPs) and specialists could be tracked for each individual patient. Therefore, a 'patient career' over time and relevant treatment costs could be identified on an individual basis in a cohort fashion. The general utilization of this data-base was admitted and approved by the data protection officer of the Ministry of Social Affairs Hesse and the data protection commissaries of AOK Hesse and KV Hesse. Only anonymous data were used for the analysis. Furthermore the German guidelines of good practice secondary data analysis were considered throughout the analyses [19].

For the assessment of costs and for the calculation of age-specific incidences, individuals of all ages with a HZ-diagnosis in 2005 to 2008 were included. To guarantee that only acute cases and costs for the first year after disease onset are included, we considered for each individual the observation period of two years (i.e. one HZ-diagnosis-free year before diagnosis, and one year after HZ-diagnosis). Hence, for cases diagnosed in 2005 we considered the year 2004 to identify and exclude non-acute cases. On the other hand for cases diagnosed in 2008 we considered 2009 to identify all relevant costs up to 12 months after the diagnosis. Therefore, the dataset contained patient data from 2004 to 2009. Costs up to one year after HZ diagnose were considered, because three month from HZ-onset are already required for the definition of PHN and PHN can persist in average for 9 month [20,13].

Identification of Herpes zoster and Postherpetic Neuralgia Cases

Definition of a HZ-case

In the data-base, all individuals with a diagnosis code according to the 'International Statistical Classification of Diseases and Related Health Problems'10th Revision (ICD-10) [21] B02.* or G53.0 between 2005 and 2008 were identified. Due to billing guidelines in the outpatient sector, the physician has to indicate the reliability of the diagnosis, in addition to the ICD-10 code. There are four types of reliability: 1.) "assured"; 2.) "conjectured"; 3.) "status after disease"; and 4.) "disease excluded". To ensure that all potential HZ-cases are considered, we included HZ-cases with respective ICD-10 codes and "assured" or "conjectured" as diagnosis reliability [22]. Outpatient diagnoses are documented by the physicians for the SHI (for reimbursement purposes) on a quarterly basis. However, for the definition of PHN-cases and for the assessment of illness-related costs the exact calendar date of HZ-diagnosis (with date of onset) was necessary. Therefore, we defined the calendar date as the date of first HZ-diagnosis based on the earliest date of one of the following conditions (no hierarchical order):

1) Date of prescription of a HZ-specific drug (e.g. virostatics or specific immunoglobulin) (Table 1); or
2) Date of prescription of pain-medication or co-analgetics by a physician, who documented the HZ-diagnosis, if there was no prescription of those drugs in the previous quarter less than four weeks before the initial prescription in the quarter of HZ-onset (Table 1). Date of acute pain medication

is a sufficient indicator, since reducing pain in the acute HZ-phase is central according to German guidelines [23]; or

3) Date of hospitalization due to HZ; or
4) Date of start of sick-leave due to HZ; or
5) Date of contact with physician, if there was only one healthcare contact or one diagnosis in the quarter of diagnosis; or
6) If none of the above-mentioned five conditions was fulfilled, we chose the first contact with the physician, who first documented the diagnosis, as the exact date of HZ-diagnosis in the quarter of diagnosis.

Cases documented with ICD10-code G53.0 (PHN) but without the HZ code B02.2 (which is not in accordance to billing guidelines for physicians) were regarded as HZ-cases.

Definition of a PHN-case

In accordance to previously published studies, we defined PHN as pain persisting at least three month after HZ-onset [24-28,13,29-31]. A HZ-patient became a PHN-case, if there was a PHN-diagnosis documentation or the initiation of a PHN-related pain therapy. Diagnoses with B02.* or G53 ICD-10 codes [21] causing hospitalization or sick-leave 3 to 6 month after the date of HZ-diagnosis were considered as a PHN-diagnosis. A PHN-related pain therapy was defined as follows:

1) Absence of a prescription of opioids, antidepressants, or anticonvulsants during the three month prior to HZ-diagnosis (Table 1), plus
2) At least one prescription of an agent listed in Table 1 within the three month after the HZ-diagnosis, plus
3) A minimum of one prescription of opioids, antidepressants, or anticonvulsants during 90 to 180 days after HZ-diagnosis (Table 1).

Perspectives and cost sectors

Costs were analyzed from the perspective of the SHI (payer perspective) as well as from the societal perspective (see Table 2). The payer perspective comprised costs for outpatient care, drug prescription, therapeutic appliance, and hospital stay. Sick-pay as transfer payments was also included in this perspective. The cost sectors for the societal perspective included all costs of the payer perspective (except for sick-pay), and in addition costs for sick-leave and patient co-payment. We accounted the HZ/PHN-related costs up to one year after disease onset.

Data for the following cost sectors were regarded:

Sick-pay (transfer payments): According to the German Social Security Code the SHI covers 70% of the insurant's gross earning per month after six weeks of work absenteeism (for the first 6 weeks the employer continues to pay the salary).

Outpatient treatment: The claims form, documented by the consulted physician, comprises the following information: Insurant's identification number (pseudonymized); quarter and year of diagnosis (ICD-10 code [21]); physician's identification number (pseudonymized); service codes with date of service. During the study period service codes were reimbursed by allowances and point values.

However, the Euro amount of one point is available after respective quarter. Since the KV of Hesse provided this data we were able to connect the service codes to the particular Euro amount paid by the SHI for each time period. Hence, we identified the potential costs for HZ and PHN-treatment in the outpatient sector. All physician groups (GP and all medical specialist groups, e.g. dermatologists and ophthalmologists) were considered. How we estimated the effective treatment costs of HZ and PHN will be described in the *'Cost-Estimation: Direct diagnosis-linkage and control-group design*' section.

Drug prescription: Each drug on a prescription can be identified by its national unique central pharmaceutical number (PZN). We linked it to the nationwide uniform pharmacy retail price (PRP) for 2010 or the drug related reference price. Table 1 presents the drugs we considered in accordance to existing treatment guidelines in Germany as relevant for the treatment of HZ and PHN [23].

Therapeutic appliance: We considered transcutaneous electrical nerve stimulation (TENS) devices and low-frequency electrical stimulation devices as relevant for pain treatment in HZ/PHN-management.

Inpatient treatment: From the data-base we used the insurant related information concerning length of hospital stay and main diagnosis. Since 2004 hospitals receive from SHI an allowance based on German Diagnosis Related Groups (G-DRG) depending on patient's age, sex and diagnosis [32]. Costs due to HZ/PHN-related hospitalization were assessed by linking the main diagnosis (reason for hospital stay) to the corresponding G-DRG and therefore to the respective Euro amount.

Sick-leave: For cost calculation the human capital approach (HCA) was applied [33]. We identified HZ/PHN-related sick-leave from ICD-10 codes [21] documented on the available sick-leave certificates together with information on duration of sick-leave. Since in German claims data more than one ICD-10 diagnose can be documented per one sick-leave episode, we included only those sick-leave episodes, if they were issued by the GP who documented the HZ/PHN-diagnosis in the quarter that covers the beginning date of the sick leave episode. Furthermore we identified sick-leave entitled individuals by their insurance status. Sick-leave entitled individuals were employed, job seeking, voluntary insured, and in rehabilitation situated individuals. We used the monthly employer's labor-costs (employee's monthly gross earnings plus employer's contribution of social insurance premium per employee, which is about 28% [34] of the employer's monthly gross earnings) on age and sex in Germany broken down on a daily basis [33,35]. These amounts were computed with the number of sick-leave days per patient. In order to estimate the costs conservatively, we utilized data from the federal statistic office of Germany, which considered both, full-time and part-time employment mean gross earnings [36].

Co-payment: The following co-payments, according to the German Social Security Code for insurance from the age of 18 were considered in this study: Outpatient contact allowance per quarter (€ 10), co-payment for certain drugs (Table 1), and therapeutic appliance (10% of price, minimum € 5 and maximum € 10, never more than the price itself). Besides drug co-payment, payers reimburse certain drugs until the reference price only. The difference between reference price and the PRP has to be paid by the insured person in addition to co-payments. Furthermore, an allowance per hospital day was considered, which is € 10 per day and has to be paid until the maximum of 28 days in hospital.

Cost-Estimation: Direct diagnosis-linkage and control-group design

Inpatient treatment, sick-pay, sick-leave, and certain parts of co-payment were services with a direct diagnosis-linkage to HZ and PHN-treatment (Table 2). However, not all drug prescriptions (e.g. pain-medication), outpatient procedures (e.g. general-counseling), therapeutic appliance (e.g. TENS devices), and co-payments (outpatient contact allowance per quarter) are HZ/PHN-specific, only. In order to estimate HZ/PHN-costs accurately, we performed a control-group design. Controls were selected and individually assigned to cases based on the following matching-variables: Age, sex, treatment costs in the year before the case was diagnosed with HZ, and sick-leave entitlement. We considered for every case one control for each service sector without direct diagnosis-linkage. The difference between treatment costs of the case and the control within the year after the HZ-diagnosis was regarded as the relevant treatment costs due to HZ/PHN. In order to separate PHN-specific costs, we computed the differences between mean costs of HZ-cases with PHN and mean costs of HZ-cases without PHN, matched according to age group, sex and sick-leave entitlement.

Statistic and Software

When considering individual cost sectors, we calculated mean costs per user of the specific service (Table 3). In the section 'total annual costs' we computed average HZ- and PHN-costs based on all HZ/PHN-cases independent from individual utilization (Table 4 and 5). To estimate total annual costs for HZ- and PHN-treatment in the SHI-population, we computed the number of cases in the SHI-population with the average costs per case and age-group from both perspectives.

Total as well as stratum-specific incidences were estimated along with 95% confidence-intervals (95%-CI). Costs per case were calculated along with bias-corrected and accelerated (BCA) intervals (95%-CI) using bootstrapping (2000 replicates) [37]. To allow extrapolation of the results from the regional SHI to the total SHI-population in Germany, all incidence and cost figures were standardized according to age and sex of the SHI-population in Germany (reference date: 31st of July 2010) [38]. We inflated all monetary amounts on Euros of 2010, by using inflation rates from the German federal office for statistics [33,39].

For better comparisons with studies from other countries, we calculated the cost findings from other countries inflated to 2010 amounts within each study's country and converted these respective amounts via the gross domestic product purchasing power parity (GDP PPP) into Euros (Germany as reference country) according to Welte et al. [40] based on data from the Organization for Economic Co-operation and Development (OECD) [41].

Software used was: SQL-Server 2000 Developer Edition 8.00.194 for Windows© 2000 professional (Microsoft, Redmond, WA, USA), SAS® (SAS Institute Inc., Cary, N.C., USA) for Windows© Release 8.2, and Microsoft Excel© 2010 (Microsoft, Redmond, WA, USA).

Results

Epidemiology

Herpes zoster Incidence

From 2005 to 2008 we identified in total 6,050 HZ-cases in our data-base, of which 5,384 (87%) had an assured diagnosis reliability. Standardized to the general SHI-population of Germany in 2010, the annual incidence over all age-groups remained stable over these 4 years. The incidence over the study period was 5.79 (95%-CI: 5.64-5.93) cases per 1,000 PY, which translates into a total of 403,625 (95%-CI: 393,237-413,013) HZ-cases annually in the total SHI-population in Germany (Table 4 and 5). With 4,436 HZ-cases, the majority of HZ-cases was 50 years of age and older. In this age-group (50+ years) the overall incidence was 9.33 (95%-CI: 9.05-9.60) HZ-cases per 1,000 PY translating into estimated 270,417 (95%-CI: 262,382-278,454) HZ-cases (67% of all HZ-cases) annually in the total SHI-population aged ≥50 years (Table 4 and 5). Figure 1 presents the incidence of HZ and the proportion of PHN among HZ-cases by age-group. In 24% of cases the PHN ICD-code G53.0 was documented without a HZ-code B02.2.

Proportion of HZ-Cases developing PHN

We identified in our data-base 301 PHN-cases. All PHN-cases were over 30 years of age and 278 of them were at least 50 years old. These figures resulted in a mean proportion of 4.5% (95%-CI: 4.0-5.0) of HZ-cases that developed PHN. Based on the estimated annual number of HZ-cases, 18,160 (95%-CI: 16,144-20,176) PHN-cases were estimated to occur within the total SHI-population in Germany each year (Table 4 and 5). Similar to the HZ-incidence, the proportion of HZ-cases developing PHN increased with age (Fig. 1): Among HZ-cases aged ≥50 years 6.0% (95%-CI: 5.3-6.7) developed PHN, which resulted in the fact that 90% of all PHN-cases can be found in this age-group (Table 4 and 5).

Costs of Illness

Utilization and costs per user

For all cost sectors, Table 3 provides an overview on the utilization of services and the mean costs per user for one year following disease onset. The results of the utilization and cost analyses are presented separately for costs related to HZ (HZ) and PHN-related costs (PHN). As presented in Table 3, the proportion of users and respective costs varied between the sectors of care and between HZ and PHN. In brief:

Sick-pay: A low proportion of HZ-cases required sick-pay (Table 3). HZ-cases younger than 30 years did not experience sick-pay. Sick-pay figures became more than 10-fold higher, when considering PHN.

Outpatient: Almost 100% of HZ-cases had at least one outpatient physician contact; among these about 90% had contact to a GP. All PHN-cases utilized outpatient treatment.

Drug prescription: About 83% of the HZ-cases and 100% of PHN-cases had drug prescriptions. While 90% of individuals over 50-years of age received drugs, only 45% of the under twenty-year old HZ-cases did.

Therapeutic appliance: With about 1% among HZ-cases and 3% among PHN-cases, this treatment option was infrequently applied in HZ/PHN-management.

Inpatient: The proportion of HZ-related hospitalization increased from 0.8% in the youngest age-group (0-9 years) to about 5% in the oldest individuals (80 years and older). These figures resulted in hospitalization rates of 2.8% of all HZ-cases and 3.2% of HZ-cases 50 years and older, respectively. On average an inpatient HZ-case spent 9.4 days in hospital. Mean duration of hospitalization was associated with age and ranged from 4 days in individuals aged <10 years to about 12 days in patients 80 years and older ($p<0.001$). The hospitalization rate among PHN-cases was about 5-fold higher compared to the rate of HZ-cases. The mean duration of PHN-related hospitalization in PHN-cases was 14 days (range: 5 days (age-group <60 years) to about 46 days (age-group 80+).

Sick-leave: About a third of employed or job-seeking HZ-cases (n=1,764, 29.2% of all HZ-cases) in our data experienced sick-leave during their disease. On average a HZ-patient experiencing sick-leave stayed 12.5 days (range: 8 days (age-group < 20 years) to about 20 days (age-group 60-69 years)) off from work (50+: 15.1 days). Individuals suffering from PHN who experienced sick-leave stayed about two months off from work (range: Over 20 days (age-group 50-59 years) to near 105 days (age-group 60-69 years)). Hence, PHN-sick-leave costs were five times higher.

Co-payment: Of all HZ-cases, 90% had to afford co-payments. In patient 50 years and older 96% had to co-finance services or treatments out of pocket. However, the average amount was below € 13 for HZ-cases and below € 39 for PHN-cases (Table 3).

Total annual Costs

Total annual HZ-related and PHN-related costs per case and the total costs extrapolated for the SHI are presented in Table 4 (payer perspective) and Table 5 (societal perspective).

From the payer perspective one HZ-case caused € 210 (95%-CI: 190-230) for HZ-treatment on average (Table 4). In addition to HZ-specific costs one PHN-case generated PHN-related costs of € 1,123 (95%-CI: 831-1,525). Based on these results, we estimated that in 2010 the SHI system in Germany was faced with a total of € 85 Million for HZ-treatment and additional € 20 Million for PHN-treatment, resulting in a total of € 105 Million (Table 4). Costs per HZ-case increased slightly with age. As a result and due to the higher number of cases in this age-group, the majority of the total costs were incurred by persons aged 50 years and older. PHN-related costs per case were higher in middle-aged individuals. Total PHN-related costs did not show a trend by age-group.

From the societal perspective, one HZ-case caused € 376 (95%-CI: 350-403) for HZ-treatment on average (Table 5). In addition to the HZ-specific costs a PHN-case generated PHN-related costs of € 1,645 (95%-CI: 1,213-2,247). When considering the societal perspective (all costs except transfer

payments) based on SHI-population figures, total costs were € 182 Million (+73%) (Table 5). HZ-related as well as PHN-related costs per case were higher in working-aged individuals than in the elderly. Despite lower incidence rates, the total costs for HZ and PHN-treatment were highest in individuals aged between 40 and 59 (€ 74 Million as compared to € 57 Million in the age-group 60-79 or € 26 Million in the age-group 20-39 years), due to costs of sick-leave.

Discussion

By utilizing a combined dataset, which contained both patient-related billing-data from one large regional SHI and patient-related treatment-documentation from one regional association of SHI-accredited physicians, we were able to describe the epidemiology of HZ and PHN and to estimate the costs related to the disease in the SHI system in Germany. With more than 400,000 incident HZ-cases annually and average costs of € 210 per HZ-case and additional € 1,123 per HZ-case, which developed PHN, the first treatment year of incident patients poses a considerable clinical and economic burden to the SHI system in Germany.

In our study population, two third of HZ-cases were 50 years of age and older. The observed incidence for people aged ≥50 years lies within the range of other studies in Germany that assessed HZ-incidence in this age-group (3.4 to 9.6 per 1,000 PY) [42,43,22]. The overall incidence of 5.8 HZ-cases per 1,000 PY for the total population is also compatible with the magnitude reported in studies from other European countries, which ranges between 3.8 and 7.9 cases per 1,000 PY [9,25,44,26,45-47]. For the US and Canada, HZ-incidences were reported in a range between 1.7 to 3.23 HZ-cases per 1,000 PY [48-51].

Based on the common PHN-definition (pain persisting at least three month after HZ-rash onset [24-28,13,29-31]), 4.5% (6.0% in people 50 years and older) of HZ-cases developed PHN in our study population. Depending on the considered age-groups in other studies, the proportion of HZ-patients developing PHN ranged between 2.6% and 14.5% in the US [3,52,51], UK [25], Germany [43], France [26], Spain[46], the Netherlands[28], Australia [53], and Italy[44].

In our population, 2.6% (3.1% in individuals 50 years and older) of HZ/PHN-patients were in hospital for an average duration of 10 days. Schiffner-Rohe et al. found a HZ-related hospitalization rate in Germany of 3.4% for HZ-patients 50 years and over [54]. The proportion of patients with HZ being hospitalized ranged in countries like France [26], UK [9], USA [51], Australia [53], and Italy [44] between 1.3% and 3%. The average length of HZ-patients being hospitalized was 7.8 to 14 days in France [26], Italy [44], and Australia [55,53].

When comparing our cost estimates to findings from a study applying a similar data-base, that consisted of data from the SHI and KV in Hesse in 2004 and the target population 50 years and older, we found lower costs per HZ-case [54]. This is mainly derived due to a lower proportion of HZ-patients being hospitalized, shorter length of hospital stay, lower costs for sick-leave due to HZ, and due to methodological differences e.g. range of included pain drugs and differences in cost assessment.

Our costs for an average HZ-cases from the payer perspective are with € 210 in the lower range of results of other industrialized countries such as the UK (PPP € 190) [56], Spain (PPP € 289)

[46], or the US (PPP € 592) [57]. In contrast, when considering costs from the payer perspective for HZ-cases in elderly, our estimated costs are more than two times higher than the estimates from UK with PPP € 93 [25]. Also the average costs per PHN-patient is in our study population more than 30% higher than in Spain (PPP € 767) [46]. By adapting all results to one equal level in terms of reference year (inflation) and GDP PPP in Euros, the residual differences might be derived, among others, from different prices, treatment procedures, and study designs.

The utilization of the AOK Hesse/KV Hesse data-base may, however, have some limitations. First, our data-base covers one region and one health insurance fund. Patients insured with the AOK in Hesse may not necessarily be representative of the German SHI-population in general since some differences between social structure and morbidity among insurances exist [58,59]. Especially findings concerning the sick-leave data may not necessarily be representative for the total German SHI population, since insurance population developed historically and there exist differences in the structure of the employment [60]. Our figures might slightly overestimate the costs of sick-leave caused by HZ, because general sick-leave statistics from an SHI type like the AOK Hesse are usually above the average in Germany [61]. And since sick-leave certificates may contain more than one ICD-10 diagnose per sick-leave episode an exact diagnose-linkage with HZ/PHN was sometimes difficulty. However, since we only included HZ/PHN sick-leave certificates if they were documented by the GP who diagnosed the HZ or PHN of the respective individual, we were able to minimize inaccuracies in the estimates of sick-leave. Furthermore, care pathways for HZ/PHN-patients may vary between regions in Germany. However, since equal services and prices are mandatory for all SHIs in Germany, since countrywide treatment guidelines for HZ and PHN exist, and since there are no substantial differences in the disease epidemiology compared to a HZ-incidence study covering almost the whole SHI in Germany [22], we believe that an extrapolation of our study results to the total SHI-population in Germany (i.e. 90% of the total population in Germany) seemed justified.

Second, we found a certain miscoding in the data-base: In a significant proportion the PHN ICD-code was documented without a HZ-code, even though billing guidelines specifically ask for it. This miscoding might be derived from a lacking uniform definition of PHN. Due to this partially inaccurate use of ICD-10 code for PHN, we were not able to identify all PHN-cases in the outpatient sector by diagnosis, but this under detection was corrected via case-identification through treatment documentation as described in the method section. Since we had to perform both, a control-group design and a PHN-cost separation step to estimate HZ/PHN-related costs, the estimated costs might differ slightly from the reality.

Third, a slight overestimation might be derived from prices for drugs, reimbursed by payer (SHI). As we considered pharmacy retail prices from public registers, we could not consider real prices paid by a SHI. Since the SHI negotiate prices for (generic) drugs with manufacturers confidentially, the real prices for drugs considered in this study might be lower.

Fourth, a proposal for health economic evaluations in Germany suggested that for the estimation of inpatient costs also capital costs per inpatient day (accounting to the societal perspective) should be considered in addition to G-DRGs [62]. However, since actual data to account

for these costs are lacking, we decided to neglect this cost factor. This might lead to an underestimation from a societal perspective.

Fifth, taking sick-pay into account has to be discussed critically. However, we considered costs for sick-pay as transfer payments, as done by Greiner [63] and by Luce et al. [64] and counted them to the payer perspective only [33]. Since sick-pay in HZ/PHN in Germany on average seems to be seldom, these costs only minimally affected costs from the payer perspective.

Finally, we were not able to estimate costs for privately paid therapy (e.g. over-the-counter drugs, acupuncture, or homeopathic treatments) from our data-base. Because this might be an important therapy option among HZ/PHN-patients, the costs from societal perspective might be even higher than estimated from our data-base. Nevertheless, the most relevant medications in HZ/PHN-therapy were considered in our study and therefore the presented results give a valid estimate for the magnitude of the costs that are related to HZ and PHN in Germany.

Besides these limitations this study holds several significant benefits. The analysis is based on a sample of over 240,000 individuals from all ages. Due to the detailed drug prescription information in the data-base we were able to use in addition to diagnosis-related codes a prescription-approach to identify potential PHN-cases. Hence, we compensated the partially incorrect PHN-diagnosis coding. Furthermore, this data-base, with its combination of SHI accounting-data and patient's treatment information, allowed very detailed cost estimations by age-groups. Hence, we were able to identify all HZ/PHN-related cost centers on a patient level. This enabled a comprehensive view on treatment pathways and cost drivers in HZ/PHN-treatment. Finally, this study is based on a multiple-year-approach. Hence, annual volatility in costs caused by political reform intervention or other causes could be counteracted. Therefore, these findings provide very detailed input data for upcoming health economic evaluations of HZ-vaccination, which will inform future decision making processes regarding a potential HZ-vaccination recommendation in Germany.

Conclusion

Our findings illustrate the epidemiological and economic impact of Herpes zoster and postherpetic neuralgia in the German healthcare system, which mainly affects individuals above 50 years of age. Due to an aging population in Germany it can be expected that the annual number of cases will increase in the future and therefore also the total costs for the healthcare system and the society. HZ- and PHN-related costs per case and total costs from the payer perspective varied by age-group but without showing a clear trend. From the societal perspective, costs per case and total costs were highest in the working-age population due to costs for sick-leave. These age-specific differences in costs need to be taken into account in future analyses when assessing the cost-effectiveness of the vaccination against HZ and PHN.

References

1. Wutzler, P., Färber, I., Wagenpfeil, S., Bisanz, H., Tischer, A.: Seroprevalence of varicella-zoster virus in the German population. Vaccine **20**(1-2), 121-124 (2001).

2. Breuer, J., Whitley, R.: Varicella zoster virus: natural history and current therapies of varicella and herpes zoster. Herpes **14 Suppl 2**, 25-29 (2007).

3. Hope-Simpson, R.E.: The Nature of Herpes Zoster: A Long-Term Study and a New Hypothesis. Proc R Soc Med **58**, 9-20 (1965).

4. Wittek, M., Doerr, H.W., Allwinn, R.: [Varicella and herpes zoster. Part 1: virology, epidemiology, clinical picture, laboratory diagnostics]. Med Klin (Munich) **105**(5), 334-338 (2010). doi:10.1007/s00063-010-1061-3

5. Schmader, K., Gnann, J.W., Jr., Watson, C.P.: The epidemiological, clinical, and pathological rationale for the herpes zoster vaccine. J Infect Dis **197 Suppl 2**, S207-215 (2008). doi:10.1086/522152

6. Drolet, M., Brisson, M., Levin, M.J., Schmader, K.E., Oxman, M.N., Johnson, R.W.et al. : A prospective study of the herpes zoster severity of illness. Clin J Pain **26**(8), 656-666 (2010). doi:10.1097/AJP.0b013e3181eef686

7. Opstelten, W., Eekhof, J., Neven, A.K., Verheij, T.: Treatment of herpes zoster. Can Fam Physician **54**(3), 373-377 (2008). doi:54/3/373 [pii]

8. Forbes, H., Thomas, S., Langan, S.: The Epidemiology and Prevention of Herpes Zoster. Current Dermatology Reports **1**(1), 39-47 (2012). doi:10.1007/s13671-011-0004-4

9. Edmunds, W.J., Brisson, M., Rose, J.D.: The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine **19**(23-24), 3076-3090 (2001). doi:S0264-410X(01)00044-5 [pii]

10. Hope-Simpson, R.E.: Postherpetic neuralgia. J R Coll Gen Pract **25**(157), 571-575 (1975).

11. Jericho, B.G.: Postherpetic neuralgia: A review. Internet Journal of Pain, Symptom Control and Palliative Care **8**(1) (2010).

12. EMA: European Public Assessment Report (EPAR) for ZOSTAVAX summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000674/WC500053462.pdf (2006). Accessed 18 March 2011

13. Oxman, M.N., Levin, M.J., Johnson, G.R., Schmader, K.E., Straus, S.E., Gelb, L.D.et al. : A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **352**(22), 2271-2284 (2005). doi:352/22/2271 [pii] 10.1056/NEJMoa051016

14. Tseng, H.F., Smith, N., Harpaz, R., Bialek, S.R., Sy, L.S., Jacobsen, S.J.: Herpes Zoster Vaccine in Older Adults and the Risk of Subsequent Herpes Zoster Disease. JAMA: The Journal of the American Medical Association **305**(2), 160-166 (2011). doi:10.1001/jama.2010.1983

15. Schmader, K.E., Levin, M.J., Gnann, J.W., McNeil, S.A., Vesikari, T., Betts, R.F.et al. : Efficacy, Safety, and Tolerability of Herpes Zoster Vaccine in Persons Aged 50–59 Years. Clinical Infectious Diseases (2012). doi:10.1093/cid/cir970

16. GlaxoSmithKline: Study to Evaluate GSK Biologicals' Herpes Zoster Vaccine GSK1437173A in Adults Aged >= 50 Years [ClinicalTrials.gov Identifier NCT01165177].

http://clinicaltrials.gov/ct2/show/NCT01165177?term=herpes+zoster&spons=GlaxosmithKline&age=12&phase=2&rank=1 (2011). Accessed 10 December 2011

17. MoH: Gesetzliche Krankenversicherung Mitglieder, mitversicherte Angehörige und Krankenstand Monatswerte Januar bis Februar 2012. http://bundesgesundheitsministerium.de/fileadmin/dateien/Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM1_Januar-Februar_2012.pdf (2012). 15 October 2012

18. Ihle, P., Köster, I., Herholz, H., Rambow-Bertram, P., Schardt, T., Schubert, I.: Versichertenstichprobe AOK Hessen/KV Hessen – Konzeption und Umsetzung einer personenbezogenen Datenbasis aus der Gesetzlichen Krankenversicherung. Das Gesundheitswesen **67**, 638-645 (2005). doi:DOI 10.1055/s-2005-858598

19. Swart, E., Ihle, P., Geyer, S., Grobe, T., Hofmann, W.: GPS--good practice secondary data analysis. Working Group for the Survey and Utilization of Secondary Data (AGENS) of the German Society for Social Medicine and Prevention (DGSMP). Gesundheitswesen **67**(06), 416-421 (2005).

20. Annemans, L., Bresse, X., Gobbo, C., Papageorgiou, M.: Health economic evaluation of a vaccine for the prevention of herpes zoster (shingles) and post-herpetic neuralgia in adults in Belgium. Journal of Medical Economics **13**(3), 537-551 (2010).

21. WHO: List of ICD-10 classifications. http://apps.who.int/classifications/apps/icd/icd10online/ (2007). Accessed 30 November 2011

22. Ultsch, B., Siedler, A., Rieck, T., Reinhold, T., Krause, G., Wichmann, O.: Herpes zoster in Germany: Quantifying the burden of disease. BMC Infectious Diseases **11**(1), 173 (2011).

23. Gross, G., Schofer, H., Wassilew, S., Friese, K., Timm, A., Guthoff, R.et al. : Herpes zoster guideline of the German Dermatology Society (DDG). J Clin Virol **26**(3), 277-289; discussion 291-273 (2003). doi:S1386653203000052 [pii]

24. Brisson, M.: Estimating the number needed to vaccinate to prevent herpes zoster-related disease, health care resource use and mortality. Can J Public Health **99**(5), 383-386 (2008).

25. Gauthier, A., Breuer, J., Carrington, D., Martin, M., Remy, V.: Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect **137**(1), 38-47 (2009). doi:S0950268808000678 [pii]
10.1017/S0950268808000678

26. Gonzalez Chiappe, S., Sarazin, M., Turbelin, C., Lasserre, A., Pelat, C., Bonmarin, I.et al. : Herpes zoster: Burden of disease in France. Vaccine **28**(50), 7933-7938 (2010).

27. Max, M., Schafer, S., Culnane, M., Smoller, B., Dubner, R., Gracely, R.: Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology **38**(9), 1427 (1988).

28. Opstelten, W., Mauritz, J.W., de Wit, N.J., van Wijck, A.J., Stalman, W.A., van Essen, G.A.: Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract **19**(5), 471-475 (2002).

29. van Hoek, A.J., Gay, N., Melegaro, A., Opstelten, W., Edmunds, W.J.: Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. Vaccine **27**(9), 1454-1467 (2009). doi:S0264-410X(08)01746-5 [pii]
10.1016/j.vaccine.2008.12.024

30. Dworkin, R.H., Portenoy, R.K.: Pain and its persistence in herpes zoster. Pain **67**(2-3), 241-251 (1996).

31. Yawn, B.P.: Post-shingles neuralgia by any definition is painful, but is it PHN? Mayo Clinic Proceedings **86**(12), 1141-1142 (2011). doi:10.4065/mcp.2011.0724

32. Schreyogg, J., Tiemann, O., Busse, R.: Cost accounting to determine prices: how well do prices reflect costs in the German DRG-system? Health Care Manag Sci **9**(3), 269-279 (2006).

33. IQWiG: Cost estimation - working paper, Version 1.0. https://www.iqwig.de/download/Working_Paper_Cost_Estimation.pdf (2009). Accessed 22 November 2011

34. DESTATIS: Lohnnebenkosten im Verhältnis zu den Bruttolöhnen und -gehältern im Jahr 2010. http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/DE/Presse/pm/2011/04/PD11__143__624,templateId=renderPrint.psml (2011). Accessed 6 February 2012

35. Krauth, C., Hessel, F., Hansmeier, T., Wasem, J., Seitz, R., Schweikert, B.: [Empirical standard costs for health economic evaluation in Germany -- a proposal by the working group methods in health economic evaluation]. Gesundheitswesen **67**(10), 736-746 (2005). doi:10.1055/s-2005-858698

36. DESTATIS: Verdienste und Arbeitskosten. In: statistics, G.f.o.f. (ed.) Verdienststrukturerhebung 2006, vol. 16/1. Wiesbaden, (2010)

37. DiCiccio, T.J., Efron, B.: Bootstrap confidence intervals. Statistical Science **11**(3), 189-228 (1996).

38. DESTATIS: Bevölkerungsfortschreibung 2010. A1 Bevölkerung am 31.12.2010 nach Alters- und Geburtsjahren. Bevölkerung insgesamt. In: office, G.f.s. (ed.). Wiesbaden, (2011)

39. DESTATIS: Consumer price overall index. http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/EN/Content/Statistics/TimeSeries/EconomicIndicators/BasicData/Content100/vpi102a.psml (2011). Accessed 8 December 2011

40. Welte, R., Feenstra, T., Jager, H., Leidl, R.: A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics **22**(13), 857-876 (2004). doi:22134 [pii]

41. OECD: Country statistical profiles. http://www.oecd.org/country/ (2011). Accessed 18 January 2012

42. Paul, E., Thiel, T.: Epidemiology of varicella zoster infection. Results of a prospective study in the Ansbach area. Hautarzt **47**(8), 604-609 (1996).

43. Schiffner-Rohe, J., Jow, S., Lilie, H.M., Köster, I., Schubert, I.: Herpes zoster in Deutschland - Eine retrospektive Analyse von GKV-Daten. MMW Fortschr Med Originalien **IV/2009**(151), 193-197 (2009).

44. Gialloreti, L., 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 **10**(1), 230 (2010).

45. Donahue, J.G., Choo, P.W., Manson, J.E., Platt, R.: The incidence of herpes zoster. Arch Intern Med **155**(15), 1605-1609 (1995).

46. Cebrian-Cuenca, A., Diez-Domingo, J., San-Martin-Rodriguez, M., Puig-Barbera, J., Navarro-Perez, J.: Epidemiology and cost of herpes zoster and postherpetic neuralgia among patients treated in primary care centres in the Valencian Community of Spain. BMC Infectious Diseases **11**(1), 302 (2011).

47. Pierik, J., Gumbs, P., Fortanier, S., Van Steenwijk, P., Postma, M.: Epidemiological characteristics and societal burden of varicella zoster virus in the Netherlands. BMC Infectious Diseases **12**(1), 110 (2012).

48. Insinga, R.P., Itzler, R.F., Pellissier, J.M., Saddier, P., Nikas, A.A.: The incidence of herpes zoster in a United States administrative database. J Gen Intern Med **20**(8), 748-753 (2005). doi:JGI05481 [pii] 10.1111/j.1525-1497.2005.0150.x

519 49. Leung, J., Harpaz, R., Molinari, N.-A., Jumaan, A., Zhou, F.: Herpes Zoster Incidence Among
520 Insured Persons in the United States, 1993-“2006: Evaluation of Impact of Varicella Vaccination.
521 Clinical Infectious Diseases **52**(3), 332-340 (2011). doi:10.1093/cid/ciq077

522 50. Tanuseputro, P., Zagorski, B., Chan, K.J., Kwong, J.C.: Population-based incidence of herpes
523 zoster after introduction of a publicly funded varicella vaccination program. Vaccine(0) (2011).
524 doi:10.1016/j.vaccine.2011.09.024

525 51. Yawn, B.P., Saddier, P., Wollan, P.C., St Sauver, J.L., Kurland, M.J., Sy, L.S.: A population-based
526 study of the incidence and complication rates of herpes zoster before zoster vaccine introduction.
527 Mayo Clin Proc **82**(11), 1341-1349 (2007).

528 52. Schmader, K.E.: Epidemiology and impact on quality of life of postherpetic neuralgia and painful
529 diabetic neuropathy. Clin J Pain **18**(6), 350-354 (2002).

530 53. Stein, A.N., Britt, H., Harrison, C., Conway, E.L., Cunningham, A., Macintyre, C.R.: Herpes zoster
531 burden of illness and health care resource utilisation in the Australian population aged 50 years and
532 older. Vaccine **27**(4), 520-529 (2009). doi:S0264-410X(08)01518-1 [pii]
533 10.1016/j.vaccine.2008.11.012

534 54. Schiffner-Rohe, J., Köster, I., Beillat, M., Lilie, H.M., Schubert, I.: Ressourcenverbrauch und
535 Kosten von Herpes zoster und postherpetischer Neuralgie in Deutschland. Gesundh ökon Qual
536 manag(EFirst) (2010). doi:10.1055/s-0029-1245896

537 55. MacIntyre, C.R., Chu, C.P., Burgess, M.A.: Use of hospitalization and pharmaceutical prescribing
538 data to compare the prevaccination burden of varicella and herpes zoster in Australia. Epidemiol Infect
539 **131**(1), 675-682 (2003).

540 56. Scott, F.T., Johnson, R.W., Leedham-Green, M., Davies, E., Edmunds, W.J., Breuer, J.: The
541 burden of Herpes Zoster: a prospective population based study. Vaccine **24**(9), 1308-1314 (2006).
542 doi:S0264-410X(05)00980-1 [pii]
543 10.1016/j.vaccine.2005.09.026

544 57. Insinga, R.P., Itzler, R.F., Pellissier, J.M.: Acute/subacute herpes zoster: healthcare resource
545 utilisation and costs in a group of US health plans. Pharmacoeconomics **25**(2), 155-169 (2007).
546 doi:2527 [pii]

547 58. Hoffmann, F., Icks, A.: Unterschiede in der Versichertenstruktur von Krankenkassen und deren
548 Auswirkungen für die Versorgungsforschung: Ergebnisse des Bertelsmann-Gesundheitsmonitors.
549 Gesundheitswesen(EFirst) (2011). doi:10.1055/s-0031-1275711

550 59. Hoffmann, F., Icks, A.: Diabetes prevalence based on health insurance claims: large differences
551 between companies. Diabetic Medicine **28**(8), 919-923 (2011). doi:10.1111/j.1464-5491.2011.03305.x

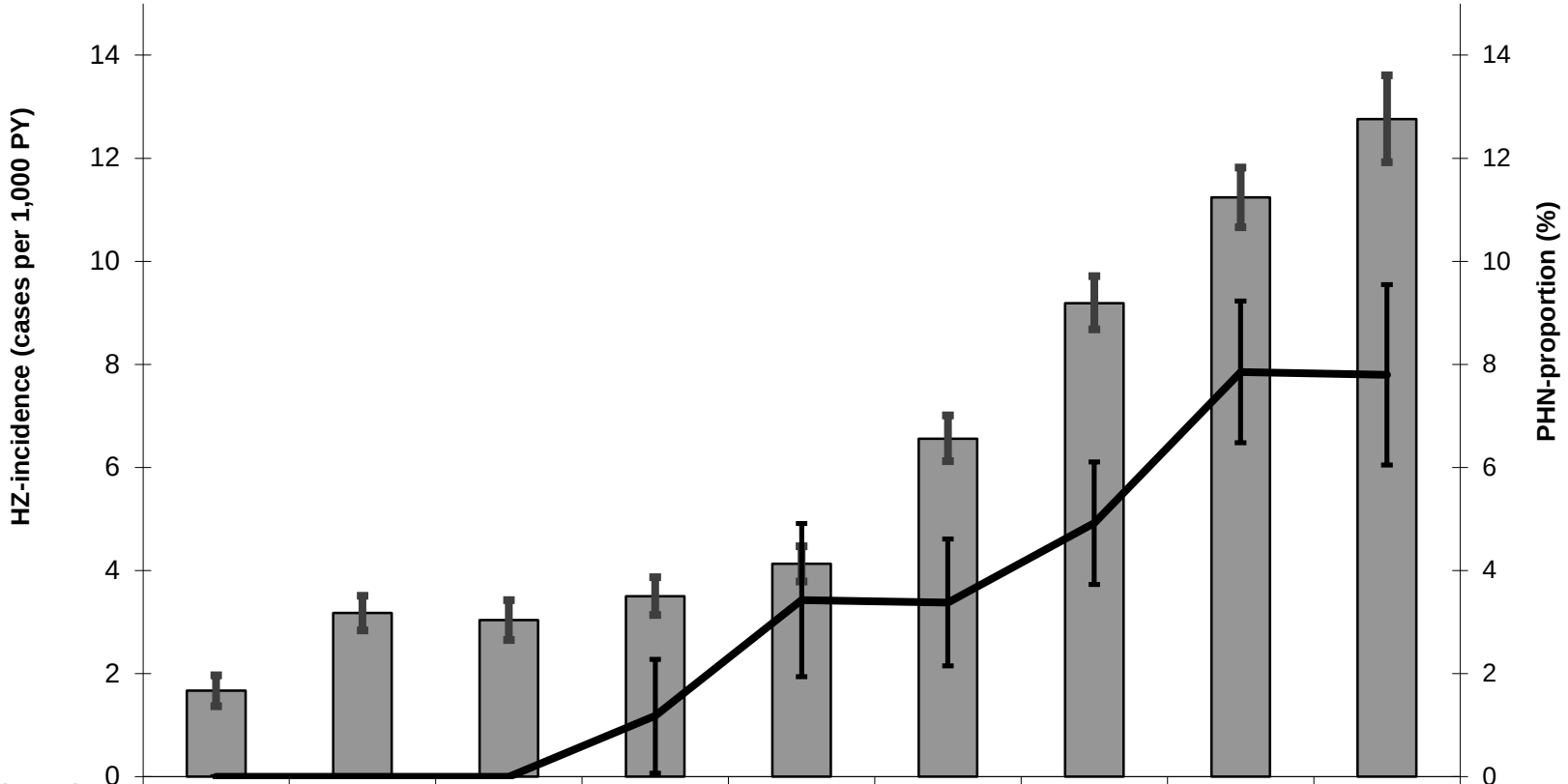
552 60. Damm, K., Lange, A., Zeidler, J., Braun, S., Graf von der Schulenburg, J.M.: Einführung des
553 neuen Tätigkeitsschlüssels und seine Anwendung in GKV-Routinedatenauswertungen.
554 Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz **55**(2), 238-244 (2012).
555 doi:10.1007/s00103-011-1418-7

556 61. Zoike, E., Bödeker, W.: Berufliche Tätigkeit und Arbeitsunfähigkeit. Bundesgesundheitsblatt -
557 Gesundheitsforschung - Gesundheitsschutz **51**(10), 1155-1163 (2008). doi:10.1007/s00103-008-0650-
558 2

559 62. Krauth, C.: Methoden der Kostenbestimmung in der gesundheitsökonomischen Evaluation.
560 Gesundh ökon Qual manag **15**(05), 251,259 (2010). doi:10.1055/s-0029-1245680

561 63. Greiner, W.: 4. Die Berechnung von Kosten und Nutzen. In: Schöffski, O., Graf von der
562 Schulenburg, J.M. (eds.) Gesundheitsökonomische Evaluation, vol. 3. Springer, Heidelberg (2008)

64. Luce, B.R., Manning, W.G., Siegel, J.E., Lipscomb, J.: Estimating Costs in Cost-Effectiveness Analysis. In: Gold, M.R., Siegel, J.E., Russell, L.B., Weinstein, M.C. (eds.) Cost-Effectiveness in Health and Medicine. Oxford University Press, New York (1996)



Age (years)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
HZ Incidence	1.67	3.18	3.04	3.5	4.13	6.56	9.19	11.24	12.76
PHN Proportion	0	0	0	1.18	3.43	3.38	4.92	7.85	7.8

Range: I = 95% confidence-interval

Fig. 1 HZ-incidence (Cases per 1,000 person years (PY)) and proportion of HZ-cases developing PHN including 95% confidence intervals.
Study period: 2005-2008, standardized based on the SHI-population in Germany

Table 1 HZ/PHN-specific Medication and ATC[a] Codes considered in the study

Medication group	Agent	ATC
Virostatics	Aciclovir[b]	J05AB01
	Famciclovir	J05AB09
	Valaciclovir	J05AB11
	Brivudine	J05AB15
Specific immunoglobulin	Idoxuridin (Zostrum)	D06BB01
Topical analgesics	Benzocaine	D04AB04/54
	Capsaicin	M02AB52 M02AP07/57
	Lidocaine	D04AB01/51
Non-opioids	Metamizole	N02BB02
	Diclofenac	M01AB05/55
	Ibuprofen	M01AE01/51
Opiods	Tramadol[b]	N02AX02/52
	Tilidine[b]	N02AX01/51
Antidepressants	Amitriptyline	N06AA09/25 N06CA01
	Imipramine	N06AA02/03
	Nortriptyline	N06AA10 N06CA06
	Desipramine	N06AA01
Anticonvulsants	Carbamazepine[b]	N03AF01
	Gabapentin[b]	N03AX12
	Pregabalin	N03AX16
	Phenytoin	N03AB02/52

[a]Anatomical Therapeutic Chemical Classification System
[b]No co-payment required
Medication according to German guidelines [27]

Table I Perspectives and Cost Sectors considered in the Study

Perspective		Cost Sector	Diagnosis-linked cost calculation
	Payer	Sick-pay (transfer payments)	Yes
Societal		Outpatient	No
		Drug prescription[#]	No
		Therapeutic appliance	No
		Inpatient	Yes
		Sick-leave	Yes
		Co-payment	No/Yes*

Modified and based on illustration in German guidelines[29];
[#i]n outpatient treatment; cost of medication in inpatient care is included in inpatient costs
*in some sectors exists a diagnose linkage in others not;

Table 3 Utilization and Costs of Herpes zoster (HZ) and Postherpetic Neuralgia (PHN) Treatment

Consumption in respective sector			Societal Perspective					
			Payer Perspective					
		Transfer payments						
		Sick-pay	Outpatient	Drug prescription	Therapeutic appliance	Inpatient	Sick-leave	Co-payment
a) Utilization [%]								
HZ[a]	**All ages**	0.2[#]	99.9	83.2	1.0	2.8	32.1[#]	89.9
	50+	0.2[#]	99.9	89.2	1.2	3.2	31.6[#]	96.0
PHN[b]	**All ages**	2.7[#]	100.0	100.0	3.4	15.4	57.3[#]	93.3
	50+	2.0[#]	100.0	100.0	3.2	14.6	45.1[#]	93.0
b) Mean annual Cost per User [€]								
HZ[c]	**All ages**	380.48	82.13	51.82	58.35	2,984.22	1,367.11	12.12
	50+	375.84	77.87	55.72	62.74	3,080.85	1,660.24	11.63
PHN[d]	**All ages**	5,453.67	185.79	210.46	48.36	3,738.21	6,529.99	36.42
	50+	4,297.04	160.23	219.79	50.96	3,890.62	6,900.65	38.04

All amounts are in Euro 2010;
Basic population: [a]HZ-cases without PHN (total: n=5,749; 50+: 4,158), [b]PHN-cases (total: n=301; 50+: 278),
[c]HZ-related costs; [d]PHN-related costs; [#]Basic: Employed or job-seeking cases (total: n=1,724; 50+: 733)

Table 4 Estimation of total annual costs due to HZ and PHN in the SHI-population in Germany – Payer Perspective

Age	Herpes zoster			Postherpetic neuralgia			Total Costs[a] in million
	Costs[a] per HZ-case (95% CI)	Number of HZ-cases[b] (95% CI)	Total HZ-costs[a] in million	Costs[a] per PHN-case (95% CI)	Number of PHN-cases[b] (95% CI)	Total PHN-costs[a] in million	
0-9	63 (12-118)	9,509 (7,809-11,209)	0.60	n.a.	n.a.	n.a.	**0.60**
10-19	129 (84-184)	22,540 (20,172-24,908)	2.90	n.a.	n.a.	n.a.	**2.90**
20-29	185 (119-273)	25,879 (22,565-29,194)	4.80	n.a.	n.a.	n.a.	**4.80**
30-39	207 (143-272)	28,485 (25,507-31,464)	5.91	1,265 (79-3,416)	341 (26-656)	0.43	**6.34**
40-49	183 (118-247)	46,794 (42,923-50,665)	8.55	1,958 (319-4,743)	1,570 (873-2,267)	3.07	**11.62**
50-59	193 (148-245)	64,250 (59,912-68,589)	12.42	872 (289-1,940)	2,172 (1,382-2,961)	1.89	**14.31**
60-69	226 (179-270)	71,036 (67,078-74,994)	16.06	1,349 (714-2,125)	3,493 (2,648-4,339)	4.71	**20.77**
70-79	203 (159-252)	83,768 (79,474-88,062)	17.01	1,172 (717-1,785)	6,578 (5,425-7,731)	7.71	**24.72**
80+	320 (249-394)	51,363 (47,951-54,775)	16.43	642 (251-1,157)	4,006 (3,105-4,908)	2.57	**19.00**
Total (50+)	**229[c] (204-256)**	**270,417 (262,382-278,454)**	**61.92**	**1,039[c] (766-1,389)**	**16,249 (14,384-18,115)**	**16.88**	**78.80**
Total	**210[c] (190-230)**	**403,625 (393,237-413,013)**	**84.67**	**1,123[c] (831-1,525)**	**18,160 (16,144-20,176)**	**20.39**	**105.06**

[a]Amounts are in Euro 2010; [b]Based on data found in our study and population figures from 2010 of Statutory Health Insurance (90% of Germany's population); [c]Mean

Table 5 Estimation of total annual costs due to HZ and PHN in the SHI-population in Germany – Societal Perspective

Age	Herpes zoster			Postherpetic neuralgia			Total Costs[a] in million
	Costs[a] per HZ-case (95% CI)	Number of HZ-cases[b] (95% CI)	Total HZ-costs[a] in million	Costs[a] per PHN-case (95% CI)	Number of PHN-cases[b] (95% CI)	Total PHN-costs[a] in million	
0-9	63 (12-118)	9,509 (7,809-11,209)	0.60	n.a.	n.a.	n.a.	**0.60**
10-19	140 (94-197)	22,540 (20,172-24,908)	3.15	n.a.	n.a.	n.a.	**3.15**
20-29	339 (258-442)	25,879 (22,565-29,194)	8.77	n.a.	n.a.	n.a.	**8.77**
30-39	547 (443-670)	28,485 (25,507-31,464)	15.57	5,993 (646-13,241)	341 (26-656)	2.04	**17.61**
40-49	603 (497-710)	46,794 (42,923-50,665)	28.20	4,288 (1,510-8,587)	1,570 (873-2,267)	6.74	**34.94**
50-59	570 (495-651)	64,250 (59,912-68,589)	36.63	1,339 (436-3,065)	2,172 (1,382-2,961)	2.91	**39,54**
60-69	338 (281-397)	71,036 (67,078-74,994)	24.04	2,137 (975-3,625)	3,493 (2,648-4,339)	7.46	**31,50**
70-79	214 (169-263)	83,768 (79,474-88,062)	17.89	1,218 (750-1,863)	6,578 (5,425-7,731)	8.01	**25,90**
80+	331 (259-408)	51,363 (47,951-54,775)	17.01	676 (270-1,207)	4,006 (3,105-4,908)	2.71	**19,72**
Total (50+)	**353[c] (322-386)**	**270,417 (262,382-278,454)**	**95.57**	**1,298[c] (911-1,743)**	**16,249 (14,384-18,115)**	**21.09**	**116.66**
Total	**376[c] (350-403)**	**403,625 (393,237-413,013)**	**151.87**	**1,645[c] (1,213-2,247)**	**18,160 (16,144-20,176)**	**29.87**	**181.74**

[a]Amounts are in Euro 2010; [b]Based on data found in our study and population figures from 2010 of Statutory Health Insurance (90% of Germany's population); [c]Mean