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Epidemiology and cost of Herpes Zoster and Postherpetic Neuralgia in Germany

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1 Abstract

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

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

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

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

21 Introduction

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

32 In 2006 the European medicine agency (EMA) licensed the first vaccine against HZ and PHN
33 for people 50 years of age and older [12]. This live-attenuated vaccine demonstrated its efficacy in a
34 randomized controlled trial including individuals aged ≥ 60 years, reducing HZ and PHN-incidence by
35 51% and 67%, respectively [13]. The vaccine's effectiveness was confirmed in a community setting in
36 the US among adults aged 60 years or older [14]. A recent clinical trial determined a vaccine efficacy
37 in preventing HZ in people aged 50-59 years by almost 70% [15]. Another vaccine candidate is
38 currently tested in a phase III clinical trial for its efficacy in preventing HZ in the elderly [16]. As of
39 2012, the licensed vaccine was not yet available on the market in most European countries. But it can
40 be expected, that the vaccine will be available on the German market in the near future.

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

44 Methods

45 *The data-base*

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

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

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

76 ***Identification of Herpes zoster and Postherpetic Neuralgia Cases***

77 **Definition of a HZ-case**

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

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

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

97 3) Date of hospitalization due to HZ; or

98 4) Date of start of sick-leave due to HZ; or

99 5) Date of contact with physician, if there was only one healthcare contact or one diagnosis in the
100 quarter of diagnosis; or

101 6) If none of the above-mentioned five conditions was fulfilled, we chose the first contact with the
102 physician, who first documented the diagnosis, as the exact date of HZ-diagnosis in the quarter of
103 diagnosis.

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

106 **Definition of a PHN-case**

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

112 1) Absence of a prescription of opioids, antidepressants, or anticonvulsants during the three month
113 prior to HZ-diagnosis (Table 1), plus

114 2) At least one prescription of an agent listed in Table 1 within the three month after the HZ-
115 diagnosis, plus

116 3) A minimum of one prescription of opioids, antidepressants, or anticonvulsants during 90 to 180
117 days after HZ-diagnosis (Table 1).

118 ***Perspectives and cost sectors***

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

125 Data for the following cost sectors were regarded:

126 *Sick-pay* (transfer payments): According to the German Social Security Code the SHI covers
127 70% of the insurant's gross earning per month after six weeks of work absenteeism (for the first 6
128 weeks the employer continues to pay the salary).

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

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

139 *Drug prescription:* Each drug on a prescription can be identified by its national unique central
140 pharmaceutical number (PZN). We linked it to the nationwide uniform pharmacy retail price (PRP) for
141 2010 or the drug related reference price. Table 1 presents the drugs we considered in accordance to
142 existing treatment guidelines in Germany as relevant for the treatment of HZ and PHN [23].

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

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

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

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

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

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

186 ***Statistic and Software***

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

192 Total as well as stratum-specific incidences were estimated along with 95% confidence-
193 intervals (95%-CI). Costs per case were calculated along with bias-corrected and accelerated (BCA)
194 intervals (95%-CI) using bootstrapping (2000 replicates) [37]. To allow extrapolation of the results from
195 the regional SHI to the total SHI-population in Germany, all incidence and cost figures were
196 standardized according to age and sex of the SHI-population in Germany (reference date: 31st of July
197 2010) [38]. We inflated all monetary amounts on Euros of 2010, by using inflation rates from the
198 German federal office for statistics [33,39].

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

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

207 **Results**

208 ***Epidemiology***

209 **Herpes zoster Incidence**

210 From 2005 to 2008 we identified in total 6,050 HZ-cases in our data-base, of which 5,384
211 (87%) had an assured diagnosis reliability. Standardized to the general SHI-population of Germany in
212 2010, the annual incidence over all age-groups remained stable over these 4 years. The incidence
213 over the study period was 5.79 (95%-CI: 5.64-5.93) cases per 1,000 PY, which translates into a total
214 of 403,625 (95%-CI: 393,237-413,013) HZ-cases annually in the total SHI-population in Germany
215 (Table 4 and 5). With 4,436 HZ-cases, the majority of HZ-cases was 50 years of age and older. In this
216 age-group (50+ years) the overall incidence was 9.33 (95%-CI: 9.05-9.60) HZ-cases per 1,000 PY
217 translating into estimated 270,417 (95%-CI: 262,382-278,454) HZ-cases (67% of all HZ-cases)
218 annually in the total SHI-population aged ≥ 50 years (Table 4 and 5). Figure 1 presents the incidence
219 of HZ and the proportion of PHN among HZ-cases by age-group. In 24% of cases the PHN ICD-code
220 G53.0 was documented without a HZ-code B02.2.

221 **Proportion of HZ-Cases developing PHN**

222 We identified in our data-base 301 PHN-cases. All PHN-cases were over 30 years of age and
223 278 of them were at least 50 years old. These figures resulted in a mean proportion of 4.5% (95%-CI:
224 4.0-5.0) of HZ-cases that developed PHN. Based on the estimated annual number of HZ-cases,
225 18,160 (95%-CI: 16,144-20,176) PHN-cases were estimated to occur within the total SHI-population in
226 Germany each year (Table 4 and 5). Similar to the HZ-incidence, the proportion of HZ-cases
227 developing PHN increased with age (Fig. 1): Among HZ-cases aged ≥ 50 years 6.0% (95%-CI: 5.3-6.7)
228 developed PHN, which resulted in the fact that 90% of all PHN-cases can be found in this age-group
229 (Table 4 and 5).

230 ***Costs of Illness***

231 **Utilization and costs per user**

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

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

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

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

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

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

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

262 *Co-payment:* Of all HZ-cases, 90% had to afford co-payments. In patient 50 years and older
263 96% had to co-finance services or treatments out of pocket. However, the average amount was below
264 € 13 for HZ-cases and below € 39 for PHN-cases (Table 3).

265 **Total annual Costs**

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

268 From the payer perspective one HZ-case caused € 210 (95%-CI: 190-230) for HZ-treatment
269 on average (Table 4). In addition to HZ-specific costs one PHN-case generated PHN-related costs of
270 € 1,123 (95%-CI: 831-1,525). Based on these results, we estimated that in 2010 the SHI system in
271 Germany was faced with a total of € 85 Million for HZ-treatment and additional € 20 Million for PHN-
272 treatment, resulting in a total of € 105 Million (Table 4). Costs per HZ-case increased slightly with age.
273 As a result and due to the higher number of cases in this age-group, the majority of the total costs
274 were incurred by persons aged 50 years and older. PHN-related costs per case were higher in middle-
275 aged individuals. Total PHN-related costs did not show a trend by age-group.

276 From the societal perspective, one HZ-case caused € 376 (95%-CI: 350-403) for HZ-treatment
277 on average (Table 5). In addition to the HZ-specific costs a PHN-case generated PHN-related costs of
278 € 1,645 (95%-CI: 1,213-2,247). When considering the societal perspective (all costs except transfer

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

284 Discussion

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

292 In our study population, two third of HZ-cases were 50 years of age and older. The observed
293 incidence for people aged ≥ 50 years lies within the range of other studies in Germany that assessed
294 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-
295 cases per 1,000 PY for the total population is also compatible with the magnitude reported in studies
296 from other European countries, which ranges between 3.8 and 7.9 cases per 1,000 PY [9,25,44,26,45-
297 47]. For the US and Canada, HZ-incidences were reported in a range between 1.7 to 3.23 HZ-cases
298 per 1,000 PY [48-51].

299 Based on the common PHN-definition (pain persisting at least three month after HZ-rash onset
300 [24-28,13,29-31]), 4.5% (6.0% in people 50 years and older) of HZ-cases developed PHN in our study
301 population. Depending on the considered age-groups in other studies, the proportion of HZ-patients
302 developing PHN ranged between 2.6% and 14.5% in the US [3,52,51], UK [25], Germany [43], France
303 [26], Spain[46], the Netherlands[28], Australia [53], and Italy[44].

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

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

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

317 [46], or the US (PPP €592) [57]. In contrast, when considering costs from the payer perspective for
318 HZ-cases in elderly, our estimated costs are more than two times higher than the estimates from UK
319 with PPP €93 [25]. Also the average costs per PHN-patient is in our study population more than 30%
320 higher than in Spain (PPP €767) [46]. By adapting all results to one equal level in terms of reference
321 year (inflation) and GDP PPP in Euros, the residual differences might be derived, among others, from
322 different prices, treatment procedures, and study designs.

323 The utilization of the AOK Hesse/KV Hesse data-base may, however, have some limitations.
324 First, our data-base covers one region and one health insurance fund. Patients insured with the AOK
325 in Hesse may not necessarily be representative of the German SHI-population in general since some
326 differences between social structure and morbidity among insurances exist [58,59]. Especially findings
327 concerning the sick-leave data may not necessarily be representative for the total German SHI
328 population, since insurance population developed historically and there exist differences in the
329 structure of the employment [60]. Our figures might slightly overestimate the costs of sick-leave
330 caused by HZ, because general sick-leave statistics from an SHI type like the AOK Hesse are usually
331 above the average in Germany [61]. And since sick-leave certificates may contain more than one ICD-
332 10 diagnose per sick-leave episode an exact diagnose-linkage with HZ/PHN was sometimes difficulty.
333 However, since we only included HZ/PHN sick-leave certificates if they were documented by the GP
334 who diagnosed the HZ or PHN of the respective individual, we were able to minimize inaccuracies in
335 the estimates of sick-leave. Furthermore, care pathways for HZ/PHN-patients may vary between
336 regions in Germany. However, since equal services and prices are mandatory for all SHIs in Germany,
337 since countrywide treatment guidelines for HZ and PHN exist, and since there are no substantial
338 differences in the disease epidemiology compared to a HZ-incidence study covering almost the whole
339 SHI in Germany [22], we believe that an extrapolation of our study results to the total SHI-population in
340 Germany (i.e. 90% of the total population in Germany) seemed justified.

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

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

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

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

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

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

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

380 **Conclusion**

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

390

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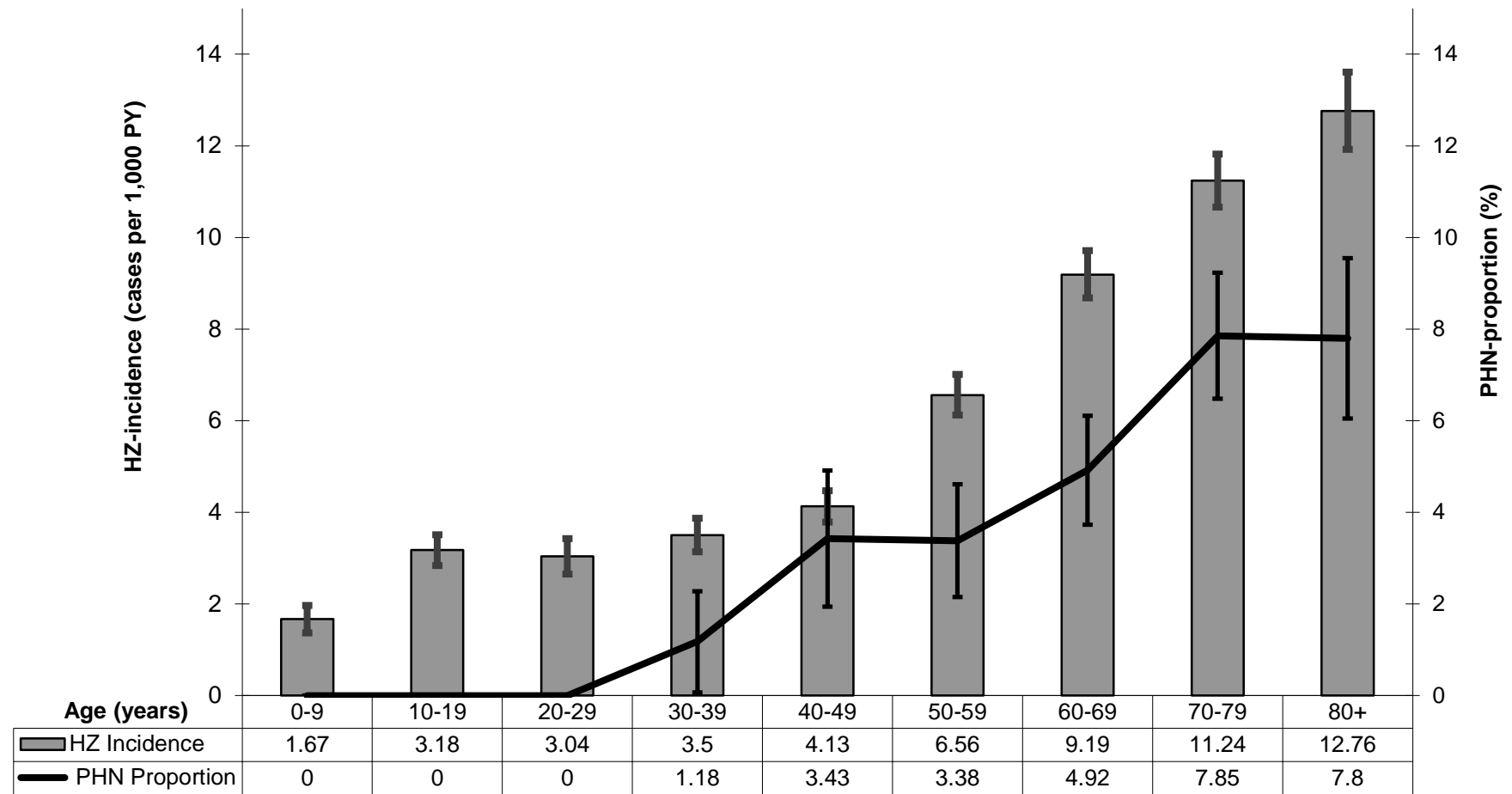
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Range: **I** = 95% confidence-interval

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 (Zostrom)	D06BB01
Topical analgesics	Benzocaine	D04AB04/54
	Capsaicin	M02AB52 M02AP07/57
	Lidocaine	D04AB01/51
Non-opioids	Metamizole	N02BB02
	Diclofenac	M01AB05/55
	Ibuprofen	M01AE01/51
Opioids	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

^aAnatomical Therapeutic Chemical Classification System^bNo co-payment requiredMedication according to German guidelines ^[27]

Table I Perspectives and Cost Sectors considered in the Study

Perspective	Cost Sector	Diagnosis-linked cost calculation
Societal	Sick-pay (transfer payments)	Yes
	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],

[#]in 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: ^aHZ-cases without PHN (total: n=5,749; 50+: 4,158), ^bPHN-cases (total: n=301; 50+: 278),

^cHZ-related costs; ^dPHN-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

^aAmounts are in Euro 2010; ^bBased on data found in our study and population figures from 2010 of Statutory Health Insurance (90% of Germany's population); ^cMean

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

^aAmounts are in Euro 2010; ^bBased on data found in our study and population figures from 2010 of Statutory Health Insurance (90% of Germany's population); ^cMean