Abstract

Background

No national vaccination program against herpes zoster (HZ) is currently in place in Norway. We aimed to quantify the burden of medically attended HZ to assess the need for a vaccination program.

Methods

We linked data from several health registries to identify medically attended HZ cases during 2008–2014 and HZ-associated deaths during1996–2012 in the entire population of Norway. We calculated HZ incidences for primary and hospital care by age, sex, type of health encounter, vaccination status, and co-morbidities among hospital patients. We also estimated HZ-associated mortality and case-fatality.

Results

The study included 82,064 HZ patients, of whom none were reported as vaccinated against HZ. The crude annual incidence of HZ was 227.1 cases per 100,000 in primary healthcare and 24.8 cases per 100,000 in hospitals. Incidence rates were higher in adults aged ≥50 years (461 per 100,000 in primary care and 56 per 100,000 in hospitals), and women than in men both in primary healthcare (267 vs 188 per 100,000), and hospitals (28 vs 22 per 100,000). Among hospital patients, 47% had complicated zoster and 25% had comorbidities, according to the Charlson comorbidity index. The duration of hospital stay (median 4 days) increased with the severity of comorbidities. The estimated mortality rate was 0.18 per 100,000; and in-hospital case-fatality rate was 1.04%.

Conclusions

Medically attended HZ poses a substantial burden in the Norwegian healthcare sector. The majority of the zoster cases occurred among adults aged ≥50 years – the group eligible for zoster vaccination – and increased use of zoster vaccination may be warranted, especially among persons with co-morbidities.

Keywords: herpes zoster, shingles, postherpetic neuralgia, burden, registries, Norway, primary healthcare, hospitalizations, deaths

Background

Herpes zoster (HZ) or shingles is a painful disease characterized by a blistering skin rash which is caused by reactivated varicella zoster virus (VZV)[1]. Usually self-limiting, HZ may result in severe complications such as postherpetic neuralgia (PHN) in 10%–50% of patients [2] and zoster ophthalmicus in 5%–14% [3, 4]. PHN, defined as a persisting pain lasting ≥30 or ≥90 days after the onset of zoster, is a particularly debilitating condition that may last for more than one year in ≥30% of patients [4] and more than five years in 2% of patients [2]. Reactivation of VZV may also cause several other neurological complications, including encephalitis, meningitis, and myelitis [5], and has been associated with an increased risk of stroke [6]. HZ and associated complications significantly impact the quality of life and result in multiple healthcare visits, hospitalizations, and deaths [7]. The lifetime risk of HZ is estimated to be 23%–30% [8]. The age-related decrease of VZV-specific cell-mediated

immunity increases the risk of disease at ages ≥50 years and the risk peaks at ages ≥80 years [9-11]. Higher risk is also reported in individuals with immunosuppression due to cancer, HIV infection, and organ transplantation [12].

Several studies have previously assessed the burden of medically attended HZ in different countries. In the US, zoster-associated General Practitioner (GP) consultation rates were 3.2 cases per 1,000 person-years with a peak of 10.9 cases per 1,000 person-years among persons ≥80 years of age [12]. In North America and Asia, hospitalization rates due to zoster ranged from 2–25 cases per 100,000 person-years, with even higher rates reported in the elderly [4]. In Western Europe, rates of HZ-associated GP consultations and hospitalizations also gradually escalate from 1–2cases per 1,000 person-years in children <10 years of age to seven to 8 cases in adults ≥50 years of age, with a peak at 10–11 cases per 1,000 person-years among 80-year-olds [8, 13]. Higher incidence rates are reported in women [8, 12, 14].

Studies from Sweden and Denmark have each reported hospitalization rates for HZ of 13 cases per 100,000 with a predominance in women [15, 16]. In Sweden, zoster associated mortality in patients ≥50 years old was 0.67 per 100,000 in women and 0.26 per 100,000 in men [16]. In Denmark, the overall standardized mortality rate was 1.8 per 100,000 [15].

Considering the magnitude of zoster burden and an increasing proportion of elderly in the European population [17], HZ vaccination may be a viable strategy to reduce the impact of HZ both for the individual and society. Currently two vaccines are licensed for prevention of shingles and PHN in adults ≥50 years old: a live-attenuated vaccine Zostavax® (Merck Sharp & Dohme Corporation, USA) and a subunit recombinant

vaccine Shingrix® (GlaxoSmithKline, Rixensart, Belgium). Zostavax®, available in Europe and in Norway since 2006, has an established efficacy and safety profile, albeit a waning vaccine protection with age has been reported [18]. Zostavax® has been little used in Norway due to a lack of endorsed national recommendations for zoster vaccination. Shingrix®, licensed in Europe in 2018, has demonstrated a promising short-term efficacy above 90% against HZ in persons aged ≥50 years, and 89% efficacy against PHN in individuals aged ≥70 years [19, 20].

At present, vaccination against HZ or varicella is not included in the national immunization program in Norway, partly due to unknown burden of disease. However, 95% of Norwegian adults ≥50 years old were reported to have detectable VZV-specific antibodies in their blood [21], and about 1.8 million are in the target group for HZ vaccination [22]. The aim of this study was to quantify the burden of medically attended HZ in Norway in order to assess the need for a vaccination program.

Materials and Methods

Study design

We conducted a national registry-based study to estimate the use of healthcare resources and mortality in patients with HZ-associated diagnoses. Given a universal access to healthcare and because children can also develop HZ, we included the entire population of Norway (5.3 million inhabitants in 2018) in the study [22]. We used individual patient data from the following national registries: the Norwegian Immunization Registry, the Norwegian Health Economics Administration, the Norwegian Patient Registry, and the Cause of Death Registry (CDR). Data were extracted for the period of 2008–2014 except for data from the CDR, which covered the period of 1996–2012. The criteria for extracted data are

63 provided in the Supplementary file 1. We linked primary care and hospital data using a unique patient identifier to determine the number of
64 patients seen in both primary and hospital care. We also linked these data to vaccination records to ascertain immunization status of each patient.

65 ***Data analysis***

66 We calculated the annual age- and sex-specific incidence rates per 100,000 population for HZ-associated diagnoses in primary and hospital care.
67 Incidence rates were calculated using the first record with a HZ-associated diagnosis for each patient registered during 2008–2014. The
68 individual patient identifier allowed us to identify all recorded HZ-associated episodes with all other registered diagnoses. Incidence rates were
69 estimated separately for each type of primary (GP or emergency) and hospital (inpatient, outpatient, ambulatory) care. The population data by
70 age, sex, and year were obtained from Statistics Norway [23]. We compared age-specific differences by sex in different patient groups by
71 performing a Kruskal-Wallis H test.

72 For hospitalized patients, registration of HZ as the primary or secondary diagnosis was recorded. In addition, for descriptive purposes, other
73 accompanying diagnoses were categorized as coded by the International Statistical Classification of Diseases and Related Health Problems, 10th
74 revision (ICD-10) (Supplementary file 2). The categorization was performed by two infectious disease specialists. We assessed the presence and
75 severity of underlying conditions by applying the Charlson comorbidity index (CCI). The CCI categorized patients into the following groups: no
76 comorbidity (score 0), moderate (score 1), severe (score 2), and very severe comorbidity (score ≥3)[15].

To examine the association between the length of hospital stay by age, sex, and a diagnostic category, we used multivariable regression analysis. We tested associations for interactions for the same factors and calculated regression coefficients for significant interactions.

To estimate HZ-associated mortality, we estimated age- and sex-standardized mortality rates per 100,000 using the World Health Organization's population data for Scandinavian countries [24]. We used Poisson regression analysis to assess seasonal trends in the numbers of HZ cases in primary healthcare, hospitals, and deaths.

We estimated the case-fatality-rate (CFR) among hospitalized HZ patients, for in-hospital deaths, and deaths occurring within 30 days post discharge.

Results

During 2008–2014, 82,064 patients were registered with a HZ-associated diagnosis in primary and hospital care in Norway, corresponding to an average annual incidence rate of 238.1 per 100,000 population. No records of zoster vaccination were identified for these patients after linkage to the national immunization registry.

Ninety-five percent of patients were treated in primary healthcare, of which 5.9% were referred to hospitals. The median age of the latter group was 73 years (IQR: 60, 82), compared to 61 years for patients in primary healthcare. An additional 4.6% of the patients had no record of contact with primary healthcare before being hospitalized.

Primary healthcare

During the study period, an average of 11,181 patients were treated in primary healthcare with a HZ-associated diagnosis annually (range: 10,030–12,304). This corresponds to an average annual incidence rate of 227.1 patients per 100,000 population (Figure 1) with a mean of 26,224 healthcare encounters each year. Among zoster patients, 68% were aged ≥50 years (median age 61 years (IQR: 42, 74)), and 59% were female. Women were significantly older (median age 62 years, IQR: 46, 75) than men (median age 59 years, IQR: 37, 71) (p<0.001). Children <10 years of age accounted for 3.2% of all cases. Zoster incidence rates in primary healthcare increased from 230.4 per 100,000 in individuals aged 50–54 years to a peak of 774.7 per 100,000 in those aged 80–84 years (Figure 1). Overall, incidence among adults ≥50 years was 460.7 cases per 100,000 (Table 1). Lowest incidence rates were in children. We observed no seasonal pattern in the distribution of HZ-associated contacts in primary healthcare.

The majority of contacts in primary healthcare were GP consultations (88.5%), and 10.7% were contacts with emergency primary care clinics, mostly outside the ordinary working hours of GPs. In 93% of the patients, HZ was the main diagnosis at the first contact, 53.8% had only one contact with primary healthcare. The remaining patients had two or more contacts (median 3 contacts (IQR: 2, 4)) and 51% were ≥50 years old.

Hospital care

During 2008–2014, an annual average of 1,218 patients (range: 1,001–1,393) with a HZ-associated diagnosis were treated in Norwegian hospitals, resulting in 2,396 hospital encounters per year, and an annual rate of 24.8 per 100,000. Most of hospital encounters (77%) were in

adults ≥50 years old (median 68 years (IQR: 52–80)), and females (56%); 73.4% of patients had zoster as the primary diagnosis at their first hospital encounter. The majority of cases were outpatients (68.9%), 27.2% were inpatients, and 3.9% received ambulatory care.

Children had the lowest hospitalization rates (Table 1, Figure 2). The rates were highest in adults ≥50 years (56 cases per 100,000) peaking at 151.1 per 100,000 in adults 85–89 years of age, mainly accounted for by inpatient cases in the latter group (Table 1, Figure 2). Inpatient and outpatient rates were similar in cases ≥50 years of age (25.8 and 29.2 per 100,000, respectively). We did not observe clear seasonal pattern in the distribution of HZ hospital cases.

Complicated HZ (ICD-10 codes: B02.0–B02.3, B02.7 and B02.8) was reported in 46.9% of hospital patients. Uncomplicated HZ was assigned to 53.1% (ICD-10 codes: B02.9 and B02), including 22.8% of patients having uncomplicated HZ as the only diagnosis (Table 2). Adults ≥50 years old accounted for 80.6% of complicated and 74.5% of uncomplicated zoster cases. Postherpetic neuralgia was found in 9.3% of hospitalized HZ patients (Table 2), 59% were females, and 81.8% were cases ≥50 years of age. Zoster ocular disease was the most frequent complication (26%), mostly affecting patients ≥50 years of age (80.9%); other reported complications included zoster encephalitis (2.9%) and zoster meningitis (0.7%) (Table 2).

Few zoster patients in primary and hospital care (0.67%, n=552) had both varicella and HZ codes, of which 35% were children <10 years of age.

Among zoster patients in hospitals, 25% had co-morbidities defined by the CCI. Severe and very severe co-morbidities were reported in approximately 15% of all patients, of which 84% were aged ≥50 years (Table 3). Patients with immunodeficiency accounted for 8.7% of hospitalized zoster cases (Table 2).

The median length of hospital stay for HZ patients was 4 days (IQR: 2, 9) (mean 7.1 days (SD: 9.709, range 1 - 242)); 5 days (IQR: 2, 9) for those ≥50 years, compared to 3.5 days (IQR:1, 7) in younger patients. Several significant interactions (particularly between age and several diagnostic groups) were identified for patients with the following conditions: diabetes (15.2 days longer stay [95% CI: 8.5 – 21.9]), kidney disorders (11.1 days longer stay [95% CI: 6.6 – 15.5]) and stroke (15.7 days longer stay: [95% CI: 6.5 – 25.0]).

HZ-associated mortality and case-fatality rate

During 1996–2012, 343 (annual range 8–27) deaths had HZ-associated ICD-codes listed as underlying (41%) or contributing cause of death (59%). All, except two deaths, occurred in persons aged ≥50 years. Estimated mortality rate using HZ as underlying cause of death was 0.18 deaths per 100,000 population per year with the highest mortality in adults aged ≥80 years, also in females (Table 4).

The case-fatality-rate (CFR) among hospitalized zoster patients was 1.04% for in-hospital deaths (annual range 0.75% –1.45%) and 3.01% for combined in-hospital deaths and deaths occurring within 30 days post-discharge.

Discussion

We estimated a pre-vaccine burden of medically attended HZ in Norway, which resulted in 11,181 (range: 10,030–12,304) primary care patients and 1,218 (range: 1,001–1,393) hospital encounters each year. The largest burden of disease was in adults ≥50 years old, a group with highest zoster incidence and more frequent hospitalizations and complications. Moreover, 99% of zoster-related deaths occurred in this age group.

Our findings are in line with reports from other European countries [8, 15, 16, 25], and may be explained by a decline in VZV-specific cell-mediated immunity with age [10, 26]. As in other studies, we also found a higher zoster incidence in women, even though cell-mediated immunity is not known to differ by sex. It is possible that lifestyle habits, psychosocial factors and healthcare seeking behavior unique to women play a role [26].

Despite differences in methodology and data used, our incidence estimates were within the reported ranges for primary healthcare [8] and hospitals from other developed countries [16, 27-31]. Although the overall hospitalization rate in Norway was higher (24 per 100,000), the rate of inpatient admissions (10.2 per 100,000) was similar to those reported by Denmark and Sweden [15, 16].

Norwegian zoster patients were hospitalized for 7.1 days on average, similarly to the findings in Denmark and Sweden [15, 16]. However, in England, the hospital stay (9.2 days) was longer despite a comparable age distribution [14]. Differences in study methods and hospital discharge practices may explain these variations in the length of hospitalization.

149 None of the patients in our study had records of HZ immunization. This is not surprising, given a low number of HZ vaccine doses distributed
150 since its licensure in Norway (approximately 200 doses during 2006–2014, unpublished data). It is however likely that some zoster vaccinations
151 were not reported to the national immunization registry, which only recently started to record immunizations with vaccines not included in the
152 national immunization program [32].

153 The estimated HZ-associated mortality and case-fatality rates in our study were low, and both estimates fall within the ranges reported from
154 other European countries [14-16, 33]. Nevertheless, our mortality estimates should be interpreted with caution. Despite a robust data coverage
155 and completeness in the Norwegian Cause of Death Registry, reporting of unspecific codes for the underlying cause of death remains high [34].
156 Moreover, the reported diagnosis on the death certificate may not always reflect the true underlying cause of death [34].

157 Our study has a number of limitations inherently linked to data sources. We used administrative claims by primary care physicians, which
158 suggests a high data completeness as primary healthcare providers in Norway are reimbursed through this system [35]. Nonetheless, not all HZ
159 patients would be captured in our data, as some may be assigned non-specific diagnoses such as “localized skin rash”. It is also possible that
160 some patients with mild HZ do not seek medical help either because they feel well enough to work or use their right to a short-term sick leave,
161 which in Norway does not require a certificate from a healthcare practitioner.

162 Another limitation of the registry data is the potential misclassification of diagnoses, which were not validated against clinical records in our
163 study. The reported completeness of individual records in the Norwegian Patient Registry has been estimated to vary between 35% and 98%
164 across different regions and for different diagnoses [36]. There might be errors due to varying coding practices among clinicians, leading to the

underestimation of the proportion of HZ diagnoses in the registry. For this reason, we included all patients with HZ listed in any diagnostic field. However, there is also a risk of overestimating the incidence of HZ when using hospital data because the diagnosis from a previous hospital stay may erroneously be carried over to subsequent unrelated hospital stays.

Several patients in our study, in particular those with multiple healthcare encounters, had both varicella and herpes zoster diagnoses, which partly may be explained by coding errors. However, clinically, it might sometimes be difficult to distinguish between these conditions [37], even though 35% of these cases were children <10 years. It was impossible to verify if these children were misclassified varicella cases. Although paediatric HZ is not common [8], the risk of developing HZ within the next four years is higher for children who acquire varicella in early childhood [38]. It is important to document the proportion of paediatric HZ cases while varicella vaccination is not universally used in Norway. Recent studies suggest a decline in paediatric zoster rates in the US after the introduction of varicella vaccination program [39].

PHN was observed in 9.3% of patients with HZ-related diagnoses, compared to 10%–50% reported elsewhere [2], but is likely underestimated in our study. Estimating the proportion of PHN based on registry data is challenging due to an unspecific diagnostic code in ICD-10, and different clinical definitions [4], thus our estimates should be interpreted with caution.

Almost 3% of HZ patients in hospital settings were diagnosed with HZ encephalitis, and this is consistent with findings from Denmark and Sweden [15, 16]. According to our previous study, VZV was the third most frequent virus among Norwegian patients with viral CNS infections, which were mostly detected in adults ≥50 years of age [40].

We found that 25% of HZ patients in the hospitals had severe to very severe comorbidities, which may be underestimated compared to 38% reported in Denmark [15]. In addition, some studies have suggested that HZ may be associated with increased risk of other conditions, such as multiple sclerosis and giant cell arteritis [41, 42].

The majority of hospitalized HZ patients in our study were immunocompetent and would be expected to have potential benefit from zoster vaccination. A recent mathematical modelling study projected a reduction in the HZ incidence after the introduction of a vaccination program with a live zoster vaccine in Norway [43]. A larger reduction was predicted with a new recombinant zoster vaccine [43]. Further research should assess the cost-effectiveness of different vaccination strategies in Norway to inform policy decision on the use of zoster vaccination.

Conclusions

Medically attended HZ poses a substantial burden in the Norwegian healthcare sector. The majority of the zoster cases occurred among adults aged ≥50 years – the group eligible for zoster vaccination – and increased use of zoster vaccination may be warranted, especially among persons with co-morbidities.

Abbreviations

CCI – the Charlson comorbidity index

CDR – the Cause of Death Registry

CFR – case-fatality-rate

CI – confidence interval

CNS – the central nervous system

GP – General Practitioner

HIV/AIDS – Human immunodeficiency virus infection and acquired immune deficiency syndrome

HZ – herpes zoster

ICD-10 – the International Statistical Classification of Diseases and Related Health Problems, 10th revision

IQR – interquartile range

NPR – the Norwegian Patient Registry

p – p-value

PHN – postherpetic neuralgia

SD – standard deviation

US – the United States of America

VZV – Varicella zoster virus

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Conflict of interests

Dr. Elmira Flem is an employee of MSD. All other authors declare that they have no conflict of interests.

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Table 1 HZ-associated primary healthcare and hospital rates per 100,000 population, Norway, 2008-2014.

	Primary healthcare		***Hospital contact***	
Age group (years)	Number of cases	Rate per 100,000	Number of cases	Rate per 100,000
Total	78266	227.11	8529	24.75
<50	24872	108.75	1944	8.5
≥50	53394	460.68	6585	56.81
0-9	2474	58.18	282	6.63
10-49	22398	120.3	1662	8.93
50-59	12049	276.9	1065	24.48
60-69	15849	438.18	1586	43.85
70-79	13784	663.16	1800	86.6
≥80	11712	758.88	2134	138.27

Table 2 Number and proportion of hospital patients (at first contact) with herpes zoster as primary or as secondary discharge diagnosis by selected diagnostic groups; and a length of hospital stay in days (coefficient, 95%CI)(n=3,758), Norway, 2008-2014.

*Coefficient represents the length of hospital stay (days) adjusted for age and sex.

	Herpes zoster at any diagnostic field		Herpes zoster as primary diagnosis		Herpes zoster as secondary diagnosis		Difference of length of hospital stay (days)			
Diagnostic group	Number of patients	%	Number of patients	%	Number of patients	%	Coefficient *	95%CI		p-value
HERPES ZOSTER patients	8529	100	6256	100	2273	100	ref	ref	ref	ref
UNCOMPLICATED HERPES ZOSTER (B02.9 and B02)	4525	53.1	3072	49.1	1453	63.9	-1.3	-1.8	-0.7	<0.000
Herpes zoster (B02)	27	0.3	23	0.4	4	0.18	na	na	na	na
Uncomplicated herpes zoster (B02.9)	4498	52.7	3049	48.7	1449	63.8	-1.3	-1.8	-0.7	<0.000
COMPLICATED HERPES ZOSTER	4004	46.9	3184	50.9	820	36.1	1.3	0.7	1.8	<0.001
HZ encephalitis, HZ meningoencephalitis (B02.0)	243	2.9	187	3.0	56	2.5	6.1	1.0	11.2	0.020
HZ meningitis (B02.1)	61	0.7	54	0.9	7	0.3	0.2	-1.9	2.3	0.851
Postherpetic neuralgia (B02.2)	790	9.3	573	9.2	217	9.6	0.7	-0.2	1.5	0.112
HZ ocular disease (B02.3)	2219	26.0	1914	30.6	305	13.4	-0.2	-1.1	0.7	0.682
HZ disseminated (B02.7)	120	1.4	86	1.4	34	1.5	4.0	1.9	6.0	<0.001
HZ with other complications (B02.8)	663	7.8	450	7.2	213	9.4	1.2	0.3	2.1	0.006
COMORBIDITIES AND OTHER CONDITIONS**	1434	16.8	634	10.1	809	35.6	3.4	2.8	4.0	<0.001
IMMUNODEFICIENCY	715	8.4	331	5.3	384	16.9	3.3	2.5	4.0	<0.001
Malignancies affecting immune system	466	5.5	211	3.4	255	11.2	2.9	2.1	3.8	<0.001
HIV/AIDS	54	0.6	18	0.3	36	1.6	0.4	-2.9	3.7	0.821
Organ transplantation	131	1.5	81	1.3	50	2.2	3.3	1.7	4.8	<0.001
Conditions affecting immune system	161	1.9	59	0.9	102	4.5	5.2	3.8	6.7	<0.001
Primary immunodeficiency	38	0.5	18	0.3	20	0.9	8.9	5.7	12.0	<0.001

AUTOIMMUNE DISEASES	432	5.1	209	3.3	223	9.8	1.7	0.7	2.7	0.001
Hematological system	8	0.1	4	0.06	4	0.2	1.8	-4.2	7.9	0.55
Endocrine system	3	0.04	3	0.05	0	0	2.3	-7.2	11.8	0.631
Central nervous / neuromuscular system	19	0.2	12	0.2	7	0.3	-1.2	-5.0	2.7	0.551
Gastrointestinal / hepatobiliary system	52	0.6	28	0.5	24	1.1	1.3	-1.2	3.8	0.295
Skin	64	0.8	25	0.4	39	1.7	3.7	0.9	6.6	0.009
Rheumatoid arthritis	102	1.2	49	0.8	53	2.3	1.0	-0.8	2.9	0.277
Juvenile rheumatoid arthritis	3	0.04	3	0.05	0	0	-2.6	-13.6	8.5	0.648
Ankylosing spondylitis	17	0.2	5	0.08	12	0.5	3.1	-2.1	8.4	0.244
Systemic lupus erythematosus	29	0.3	16	0.3	13	0.6	2.2	-1.7	6.0	0.265
Mixed connective tissue diseases	1	0.01	1	0.02	0	0	-3.3	-12.8	6.3	0.503
Sjögren´s syndrome	14	0.2	4	0.06	10	0.4	-0.9	-8.7	6.8	0.813
Sarcoidosis	12	0.2	4	0.06	8	0.4	8.9	3.1	14.6	0.002
Vascular diseases	64	0.8	31	0.5	33	1.5	0.8	-1.5	3.2	0.487
Ocular diseases	56	0.7	33	0.5	23	1.0	1.0	-4.6	6.5	0.736
Pulmonary system	12	0.1	5	0.08	7	0.3	2.2	-3.1	7.5	0.415
Diabetes	321	3.8	156	2.5	165	7.3	2.3	1.3	3.3	<0.001
Kidney disorders	380	4.4	160	2.6	220	9.7	3.3	2.3	4.2	<0.001
Dialysis	29	0.3	10	0.2	19	0.8	8.8	5.7	11.7	<0.001
Pregnancy	10	0.1	4	0.06	6	0.3	-3.2	-9.0	2.6	0.279
Neurological conditions	321	3.8	182	2.9	139	6.1	1.6	0.6	2.5	0.002
Other malignancies	453	5.3	154	2.5	299	13.2	3.0	2.1	3.9	<0.001
Liver disorders	18	0.2	5	0.08	13	0.6	3.6	-0.3	7.4	0.067
Stroke	162	1.9	62	1.0	100	4.4	3.9	2.5	5.3	<0.001

*Coefficients in the table are estimates of differences in length of hospital stay in days for moderate, severe, and very severe co-morbidities and adjusted for age and sex.

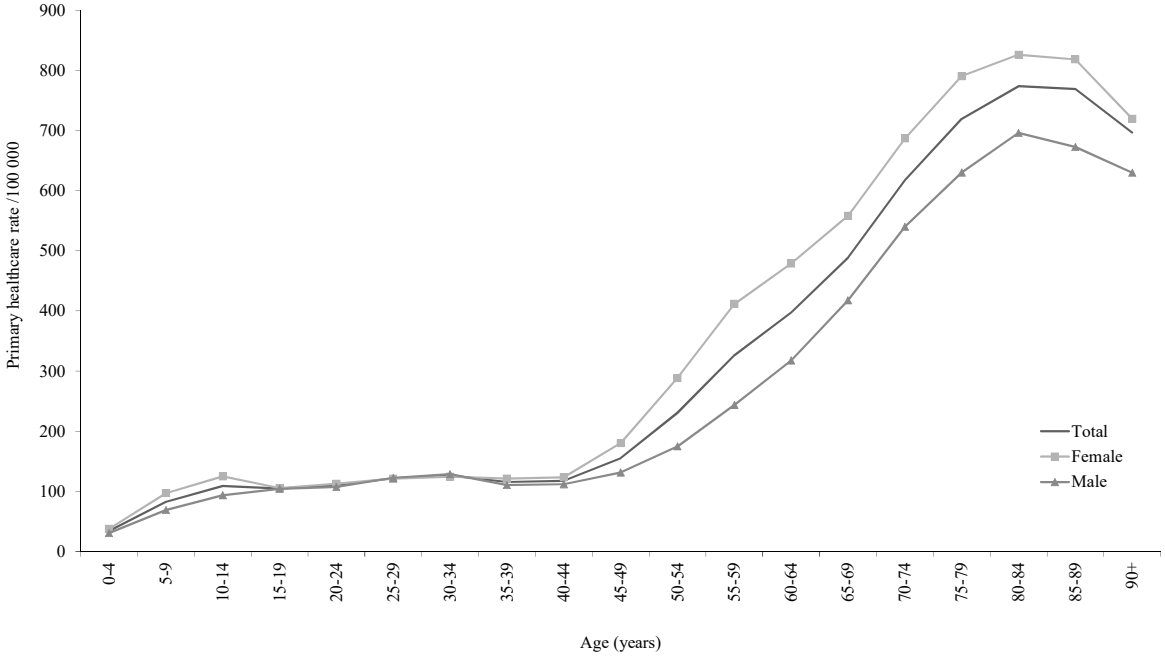
Table 3 The proportion (%) of comorbidities among hospitalized patients with HZ-related ICD-10 codes on discharge diagnoses according to the Charlson comorbidity index by age (years), severity, and difference in the length of hospital stay (days), Norway, 2008–2014.

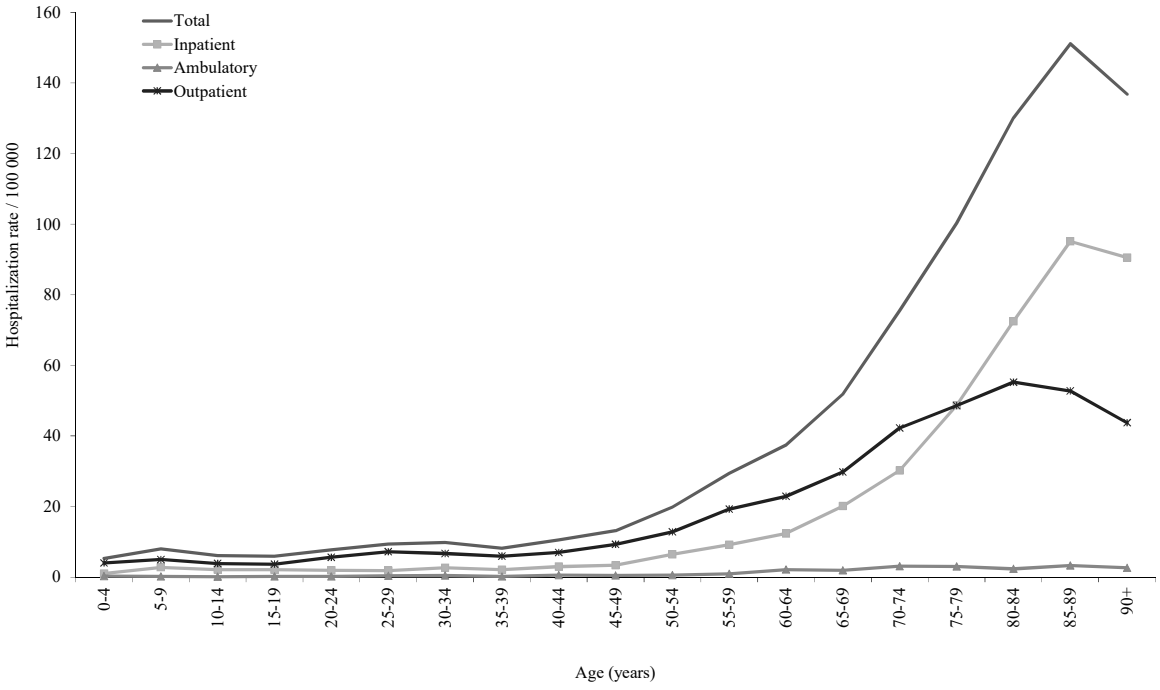
**The category includes ICD-10 codes registered on hospital discharge diagnoses for patients with HZ diagnosis.

Age group (years)	Total		0–19y		20–49y		50–59y		60–69y		70–79y		80y+					
Comorbidity Severity	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	Coeff.*	95% CI		p-value
None	6373	74.7	440	5.2	1260	14.8	849	10.0	1174	13.8	1263	14.8	1387	16.3	Ref	Ref	Ref	Ref
Moderate	878	10.3	10	0.1	31	0.4	54	0.6	122	1.4	252	3.0	409	4.8	2.5	1.8	3.3	<0.001
Severe	1062	12.5	90	1.1	69	0.8	126	1.5	224	2.6	244	2.9	309	3.6	4.3	3.6	5.0	<0.001
Very severe	216	2.5	9	0.1	35	0.4	36	0.4	66	0.8	41	0.5	29	0.3	4.8	3.5	6.1	<0.001
Total	8529	100	549	6.4	1395	16.4	1065	12.5	1586	18.6	1800	21.1	2134	25.0				

Table 4 Crude and age- and sex-adjusted mortality rates associated with herpes zoster diagnosis (ICD-10) as underlying or contributing cause of death, Norway, 1996–2012.

	Crude HZ mortality per 100,000			Standardized HZ mortality per 100,000		
Age group (years)	Total	HZ as underlying cause of death	HZ as contributing cause of death	Total	HZ as underlying cause of death	HZ as contributing cause of death
<50	0.00	0.00	0.00	0.00	0.00	0.00
50–59	0.08	0.01	0.07	0.01	0.00	0.01
60–69	0.19	0.04	0.14	0.02	0.00	0.01
70–79	0.71	0.27	0.44	0.04	0.01	0.02
≥80	8.13	3.48	4.65	0.16	0.07	0.09
Sex						
Female	0.56	0.26	0.30	0.28	0.13	0.15
Male	0.31	0.10	0.21	0.15	0.05	0.10
Total	0.43	0.18	0.26	0.43	0.18	0.26


900
800
700
600
500
400
300
200
100
0
Primary healthcare rate /100 000
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
Age (years)
Total
Female
Male


Total
Inpatient
Ambulatory
Outpatient
Hospitalization rate / 100 000
160
140
120
100
80
60
40
20
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
Age (years)