Acta Derm Venereol 2009; 89: 612–616

INVESTIGATIVE REPORT

Epidemiological Features and Costs of Herpes Zoster in Taiwan: A National Study 2000 to 2006

Jaw-Shyang JIH[1,2], Yi-Ju CHEN[1,3], Ming-Wei LIN[4,5], Yu-Chun CHEN[6,7], Tzeng-Ji CHEN[6,7], Yu-Lin HUANG[1,2], Chih-Chiang CHEN[1,2], Ding-Dar LEE[1,2], Yun-Ting CHANG[1,2,8], Wen-Jen WANG[1,2] and Han-Nan LIU[1,2,9]

Departments of [1]Dermatology, [4]Institute of Public Health, [6]Faculty of Medicine, National Yang-Ming University, Departments of [2]Dermatology, [5]Medical Research and Education, [7]Family Medicine, Taipei Veterans General Hospital, [3]Department of Dermatology, Taichung Veterans General Hospital, Taichung, [8]Department of Dermatology, National Yang Ming University Hospital, I-Lan and [9]Department of Dermatology, National Defence Medical Center, Taipei, Taiwan

To analyse the epidemiological characteristics and related costs of herpes zoster in Taiwan, a nationally representative cohort of 1,000,000 individuals from the National Health Insurance register was followed up from 2000 to 2006 and their claims data analysed. Overall, 34,280 patients were diagnosed with zoster (incidence 4.89/1000 person-years) and 2944 patients (8.6%) developed post-herpetic neuralgia 3 months after the start of the zoster rash (incidence 0.42/1000 person-years). People with older age, diabetes, and immunocompromising conditions were at higher risk of developing zoster and post-herpetic neuralgia. The overall hospitalization rate for zoster was 16.1 cases per 100,000 person-years. The cost for each home care case and per hospitalized case were approximately €53.30 and €1224.70, respectively. Further research into the cost-effectiveness of zoster vaccine is needed. ***Key words: cost; epidemiology; herpes zoster; post-herpetic neuralgia.***

(Accepted June 8, 2009.)

Acta Derm Venereol 2009; 89: 612–616.

Yun-Ting Chang, Department of Dermatology, Taipei Veterans General Hospital, Shih-Pai, 112 Taipei, Taiwan. E-mail: ytchang@vghtpe.gov.tw

Herpes zoster (HZ) or shingles is a clinical manifestation caused by activation of the varicella-zoster virus (VZV) that has remained latent in the sensory ganglia and dorsal nerve roots following varicella infection. This disease is characterized by a unilaterally grouped vesicular rash with radicular pain, which is generally limited to a single dermatome (1, 2). The estimated lifetime risk of developing zoster in those exposed to varicella is 10–30%, while the incidence and severity of HZ increases with age; more than 50% of all persons in whom HZ develops are older than 60 years (3–5). The most common complication of HZ is post-herpetic neuralgia (PHN), which has been variably defined as any pain one month, 3 months, or 4 months after rash onset (6, 7). Possible risk indicators for the occurrence of PHN include older age, female sex, presence of a prodrome, greater rash severity, and greater acute pain (6).

In Europe and the USA, the incidence of HZ is 1.2–4.8 cases per 1000 person-years (8). However, to the best of our knowledge, the epidemiology of HZ and PHN has not been well investigated in Asia. In Taiwan, the National Health Insurance (NHI) programme covers most of the population (the coverage rate in 2000 was 96.16%). Most medical institutions (93%) have been contracted to the Bureau of NHI. Inhabitants of Taiwan are free to choose Western medicine or traditional Chinese herbal medicine, and can choose to visit either public or private medical facilities (9). Therefore, information from the NHI database is considered appropriate for assessment of epidemiological features of HZ in Taiwan. The objectives of this study are to estimate the epidemiological characteristics of HZ in Taiwan, to describe the Western and Chinese herbal management of cases, and to calculate the costs of home care and hospital care based on the NHI reference costs.

PATIENTS AND METHODS

We conducted a retrospective cohort study based on the NHI programme. The NHI programme was initiated in Taiwan in 1995 and covers almost all of the population (21,653,555 beneficiaries at the end of 2001, equivalent to a coverage rate of 96.6%). In 1999, the Bureau of NHI began to release all claims data in electronic format to the public under the National Health Insurance Research Database (NHIRD) project, and NHIRD has been used extensively in many epidemiological studies (10, 11).

In the present study, a total of 1,000,000 persons (approximately 5% of Taiwan's population), were randomly selected from Taiwan's NHIRD. Data from 495,816 men (49.5%) and 504,184 women (50.4%) were evaluated. Attrition of the study cohort was observed due to various reasons such as mortality and emigration. We linked, through individuals' personal identification numbers, to both the ambulatory care and inpatient claims in order to identify all cases of HZ. The NHI electronic data files provided patient identification numbers, gender, date of birth, diagnostic codes, prescription drugs dispensed, medical cost, medical care facilities and specialties. Cases were defined with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code as zoster (from 053.0 to 053.9) present in either an inpatient or outpatient service claim. We used the claims data for the years 2000 to 2006 to investigate the incidence rate, demographic characteristics, treatment modalities, risk factors, and economic burden of patients with HZ. PHN was defined as visiting a physician again with a coding of zoster more than 90 days after the first onset in addition to receiving treatment for neuralgia.

For each cohort year, the incidence was calculated as the number of patients with HZ divided by the total population of that cohort year. After analysing our database and reviewing documents and journals, the following diseases were considered as possible co-morbid diseases associated with HZ: diabetes mellitus (DM) (ICD-9 code 250), systemic lupus erythematosus (SLE) (ICD-9 code 710), human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (ICD-9 codes 042), breast cancer (ICD-9 code 174-175), liver cancer (ICD-9 code 155), and lymphoma//leukaemia (ICD-9 code 200–202 and 204–208).

The NHI provides comprehensive coverage, including outpatient/in-patient care, laboratory tests, prescription drugs, etc. The additional expense of NHI enrollees includes payment for services not covered by the NHI as well as "user fees" and "co-payments" for NHI-covered services. The medical care expenditure data used in the present study include medical expenditures of outpatient services and hospitalization of the study subjects. All medical costs presented in the study were then converted from Taiwan dollars ($NT) to Euros using an exchange rate of 31.07:1, based on the average exchange rate during 2000 to 2006. The study was approved by the institution review board of the hospital.

Data were analysed using SAS statistical software (Version 8.2; SAS Institute, Cary, NC, USA), SPSS (Version 15; SPSS Inc.) and Excel (Microsoft Office 2007). We used a Poisson regression model with age, sex, and each possible associated disease as covariates to analyse their association with HZ and PHN. Rate ratios (RRs) and 95% confidence interval (CI) from the Poisson regression model after controlling for each of the other covariates in the model were used to estimate the magnitude of the association between risk factors and HZ/PHN. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Demographic data of patients with zoster

In this study cohort, there were 34,280 patients (16,332 males and 17,948 females) with a claim of primary diagnosis of HZ during the 7-year study period. Among these patients with HZ, 18,569 cases (56%) were diagnosed by dermatologists, followed by family doctors (9%) and internists (7%). A total of 11,421 patients (33.3%) were 60 years or older. The incidence rate of HZ in all age groups was 4.89 cases/1000 person-years (Fig. 1). There was no significant gender difference in the incidence of HZ in Taiwan (Females: 5.09 cases/1000 person-years; Males: 4.71 cases/1000 person-years). When the results were stratified according to age, it was found that the incidence increased with age. The highest incidence rate was in patients over 80 years of age (13.69 cases/1000 person-years), while the lowest (2.07 cases/1000 person-years) in patients younger than 20 years. Overall, 1125 patients were admitted with HZ discharge diagnosis. The hospitalization rate for HZ was 16.1 per 100,000 person-years. The largest proportion (59.5%) of hospitalizations was in adults older than 60 years of age. The average number of inpatient days per zoster admission was 8.3 days, and this increased with age from 6.06 days in 0–20 year olds to 9.19 days in elderly people (over 60 years of age).

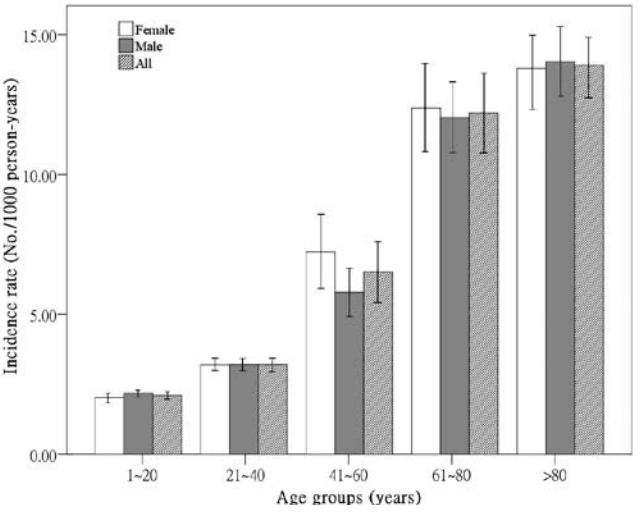

Fig. 1. Age- and sex-specific incidence rate (and 95% confidence intervals) of herpes zoster during 2000 to 2006 in Taiwan.

Co-morbid diseases

The co-morbid diseases in patients with HZ included DM (7062 cases, 20.60%), lymphoma/leukaemia (233 cases, 0.68%), breast cancer (314 cases, 0.92%), liver cancer (388 cases, 1.13%), SLE (284 cases, 0.83%), and HIV/AIDS (61 cases, 0.18%). A multivariate Poisson regression model demonstrated that patients with HZ were more likely to have DM, lymphoma/leukaemia, breast cancer, liver cancer, SLE, and HIV/AIDS even after controlling for confounders, including age, sex, and other potential risk factors (Table I).

Post-herpetic neuralgia

A total of 4543 patients (13.3%) had persistent neuralgia one month after the start of the zoster rash (incidence 0.64/1000 person-years) and 2944 patients (8.6%) developed PHN 3 months after the start of the zoster rash (incidence 0.42/1000 person-years) (Fig. 2). Zoster patients 60 years or older were more likely to develop PHN than those younger than 60 years (RR: 2.34) (Table II). Moreover, more than 20% of zoster patients over 80 years old would develop PHN. In contrast, the frequency of developing PHN was similar

Table I. *Multivariate analysis for the co-morbid diseases in patients with herpes zoster vs. controls*

Co-morbid diseases	RR (95% CI)[a]	p-value
Diabetes mellitus	1.522 (1.478–1.565)	<0.001
Lymphoma/leukaemia	1.908 (1.670–2.179)	<0.001
Breast cancer	1.568 (1.399–1.758)	<0.001
Liver cancer	1.191 (1.076–1.318)	<0.001
Systemic lupus erythematosus	2.115 (1.876–2.385)	<0.001
HIV/AIDS	1.527 (1.172–1.990)	<0.001

[a]Model adjusted for age and sex.
RR: rate ratio; CI: confidence interval; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

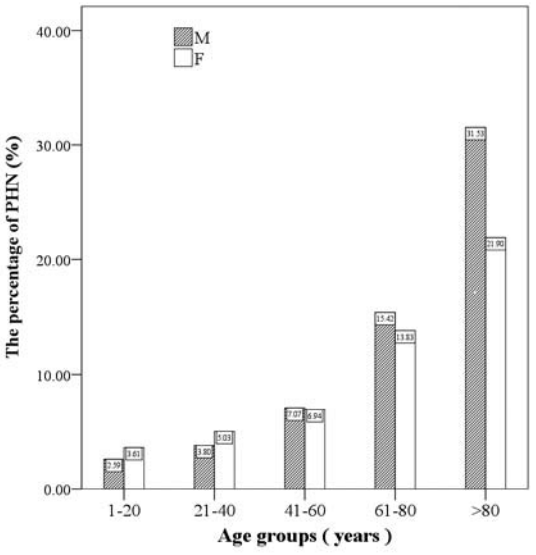

Fig. 2. Percentage of post-herpetic neuralgia (PHN) in patients with herpes zoster.

in males and females (8.82% vs. 8.37%). Other independent risk factors for PHN included diabetes (RR: 1.35), lymphoma/leukaemia, and SLE.

Management of the disease

Table III shows the distribution of prescribed drugs and other treatment modalities, including acupuncture and herbal medicine. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most frequently prescribed medications, and were used by 61.1% of patients. The other common treatments included acetaminophen (49.3%), topical and systemic antiviral agents (23.6%), systemic corticosteroids (14.7%), tricyclic antidepressants (8.9%), anticonvulsants (6.6%), and opiates (3.9%). A minority (3.6%) of patients also took Chinese herbal medicine and 0.3% received acupuncture.

Medical care expenditure

The total cost of the 34,003 home care HZ cases was €1,811,603.80 and the cost per case was €53.30 ($NT1655). On the other hand, the total cost of the 1125 hospitalized cases was €1,377,791 and the cost per treated hospitalized case was €1224.70 ($NT38,051). With a mean inpatient stay of 8.3 days, the average expenditure per treated case was €147.60 per day. Further analysis by age groups showed that patients 60 years or older accounted for 59.5% of the total medical care costs.

Table II. *Multivariate analysis for potential risk indicators for post-herpetic neuralgia at 3 months in patients with herpes zoster*

Potential risk indicator	RR (95% CI)[a]	*p*-value
Age ≥60 years	2.344 (2.171–2.532)	<0.001
Female gender	0.953 (0.886–1.025)	0.195
Diabetes mellitus	1.351 (1.246–1.467)	<0.001
Lymphoma/leukaemia	1.735 (1.319–2.282)	<0.001
Breast cancer	0.748 (0.526–1.063)	0.105
Liver cancer	0.864 (0.651–1.148)	0.315
Systemic lupus erythematosus	2.268 (1.749–2.942)	<0.001
HIV/AIDS	0.475 (0.264–0.856)	0.013

[a]Model adjusted for age and sex.
RR: rate ratio; CI: confidence interval; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

Table III. *Treatment modalities in Taiwanese patients with herpes zoster*

Treatment modalities	% of zoster patients
NSAIDs	61.1
Acetaminophen	49.3
Antiviral agents	23.6
Topical antiviral agent	13.4
Systemic antiviral agent	12
Systemic corticosteroid	14.7
TCA	8.9
Anticonvulsants	6.6
Carbamazepine	5.2
Gabapentin	1.9
Opiates	3.9
Chinese herbal medicine	3.6
Topical NSAIDs	2.1
Acupuncture	0.3
Lidocaine cream	0.1

NSAIDs: non-steroidal anti-inflammatory drugs; TCA: tricyclic antidepressants.

DISCUSSION

Unlike other population-based studies (12), the incidence of HZ in Taiwan was estimated not only on the basis of general practitioner, but patients visiting medical centres and dermatologists, have been included in the study. According to our results, the incidence rate of HZ in Taiwan was 4.89 cases/1000 person-years in all age groups and 13.69 cases/1000 person-years in persons over 80 years of age. This incidence is comparable to the results published in Caucasian-based studies (1.2–4.8/1000 person-years) (13–15). To the best of our knowledge, there is no large population-based study of epidemiology of HZ in Asia except for one study in South Korea (16). That study was performed in military personnel and revealed that the annual incidence rate of HZ was 1.41 per 1000 population. However, this study was probably of limited value because only young adult males were enrolled.

Several studies have demonstrated that people with suppressed cell-mediated immunity from immunosuppressive diseases are at higher risk of zoster. In the present study, although most cases showed no risk factors for HZ, malignancy, SLE, and HIV/AIDS were noted in 2.73%, 0.83%, and 0.18% of our cases, respectively. Moreover, DM was found in 20.60% of our cases and multivariate analysis confirmed DM as an independent risk factor for HZ. In fact, a recent

study from Israel also suggested that DM was often accompanied by impaired cell-mediated immunity and carried increased risk of HZ (17). Although a previous study reported that female gender was an independent risk factor for HZ (18), there was no significant gender difference in the incidence of HZ in Taiwan.

The incidence of PHN in our study was 0.42 cases/1000 person-years. Studies worldwide showed that the incidence, severity, and complications of HZ all increased with age (6, 7, 19–24). Possible risk indicators for the occurrence of PHN include older age, female sex, presence of a prodrome, greater rash severity, and greater acute pain (6). Our results also showed that zoster patients 60 years or older were more likely to develop PHN than persons younger than 60 years and DM was an independent risk factor for PHN. In contrast, the frequency of developing PHN was similar in males and females. As the data of rash severity and pain intensity were not available in the NHI database, we were unable to clarify their relationship with PHN.

Our study showed that the majority of patients received NSAIDs or acetaminophen. Other common therapy included antiviral agents (23.6%), systemic corticosteroids, and tricyclic antidepressants. Because the expense of using antiviral agents was covered by the NHI programme only in severe HZ infections, many patients might pay for the treatment privately. In Taiwan, Chinese herbs and acupuncture were prescribed in 3.6% and 0.3% of cases, respectively. However, further studies are needed to prove the efficacy of Chinese medicines in the treatment of HZ.

The management of HZ and its complications causes a large economic burden. Compared with the cost of HZ in Europe, the expenditure of HZ is lower in Taiwan. The cost of each home care case was €136.10 in Italy, but €53.30 in Taiwan. The cost of each hospitalized case was €4082.60 in Italy and €1224.70 in Taiwan (25). In Taiwan, a varicella vaccination programme was implemented in 2004. It was suggested that as varicella vaccine coverage in children increased, the incidence of varicella would decrease and the occurrence of HZ might increase (26). However, studies monitoring HZ incidence in the USA have shown inconsistent findings (27). Further study is required to investigate whether the zoster incidence will change after long-term varicella vaccination in Taiwan. A recent study also showed that zoster vaccine was efficacious in reducing the morbidity related to HZ in the immunocompetent elderly population (28). Another study revealed that the cost-effectiveness of zoster vaccine varied substantially with patient age and often exceeded $100,000 per quality-adjusted life year saved (29). As the zoster vaccine is currently not available in Taiwan, our study has provided the background data of HZ and further studies focused on the cost-effectiveness of HZ vaccine in Taiwan are warranted.

There are some limitations of this study. As patients with mild zoster may not have visited a doctor, it is probable that the incidence of mild zoster may be underestimated. It is also likely that people with co-morbid conditions are more likely to present to medical care, which may therefore cause bias.

In conclusion, this is the first large-scale epidemiological study of HZ in Asia and it provides information on the basic epidemiological features and impact of HZ in Taiwan.

ACKNOWLEDGEMENTS

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes in Taiwan. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

This study was supported by a grant from Taipei Veterans General Hospital (VGH V98C1-066), Executive Yuan, Taiwan, ROC.

REFERENCES

1. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 1965; 58: 9–20.
2. Gnann J-WJ, Whitley R. Clinical practice. Herpes zoster. N Engl J Med 2002; 347: 340–346.
3. Bowsher D. The lifetime occurrence of herpes zoster and prevalence of postherpetic neuralgia: a retrospective survey in an elderly population. Eur J Pain 1999; 3: 335–342.
4. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 2001; 127: 305–314.
5. Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med 1983; 309: 1434–1440.
6. Jung BF, Johnson RW, Griffin DR, Dworkin RH. Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology 2004; 62: 1545–1551.
7. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract 2002; 19: 471–475.
8. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 2004; 4: 26–33.
9. Chen FP, Chen TJ, Kung YY, Chen YC, Chou LF, Chen FJ, Hwang SJ. Use frequency of traditional Chinese medicine in Taiwan. BMC Health Serv Res 2007; 7: 26.
10. Health and National Health Insurance Annual Statistics Information Services. Available from: http: //www.nhi.gov.tw/english/index.asp
11. Kuo HW, Tsai SS, Tiao MM, Yang CY. Epidemiological features of CKD in Taiwan. Am J Kidney Dis 2007; 49: 46–55.
12. Scott FT, Johnson RW, Leedham-Green M, Davies E, Edmunds WJ, Breuer J. The burden of herpes zoster: a prospective population based study. Vaccine 2006; 24: 1308–1314.

13. Chapman RS, Cross KR, Fleming DM. The incidence of shingles and its implication for vaccination policy. Vaccine 2003; 21: 2541–2547.
14. Czernichow S, Dupuy A, Flahault A, Chosidow O. Herpes zoster: incidence study among sentinel general pratictioners. Ann Dermatol Venereol 2001; 128: 497–501.
15. Chidiac C, Bruxelle J, Daures JP, Hoang-Xuan T, Morel P, Leplège A, et al. Characteristics of patient with herpes zoster on presentation to practitioners in France. Clin Infect Dis 2001; 33: 62–69.
16. Kang CI, Choi CM, Park TS, Lee DJ, Oh MD, Choe KW. Incidence of herpes zoster and seroprevalence of varicella-zoster virus in young adults of South Korea. Int J Infect Dis 2008; 12: 245–247.
17. Heymann AD, Chodick G, Karpati T, Kamer L, Kremer E, Green MS, et al. Diabetes as a risk factor for herpes zoster infection: results of a population-based study in Israel. Infection 2008; 36: 226–230.
18. Opstelten W, Van Essen GA, Schellevis F, Verheij TJ, Moons KG. Gender as an independent risk factor for herpes zoster: a population-based prospective study. Ann Epidemiol 2006; 16: 692–695.
19. Schmader K. Herpes zoster in older adults. Aging Infect Dis 2001; 32: 1481–1486.
20. Johnson R, Whitton, TL. Management of herpes zoster (shingles) and postherpetic neuralgia. Expert Opin Pharmacother 2004; 5: 551–559.
21. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract 1975; 157: 571–675.
22. Schmader K. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002; 18: 350–354.
23. Strauss S, Oxman, MN, Schmader KE, editors. Fitzpatrick's dermatology in general medicine. 7th edn. Vol. 2. New York, NY: McGraw-Hill; 2008, p. 1885–1898.
24. Johnson R, Dworkin, RH. Treatment of herpes zoster and postherpetic neuralgia. BMJ 2003; 326: 748–750.
25. Di Legami V, Gianino MM, Atti MC, Massari M, Migliardi A, Tomba GS, et al. Zoster Study Group. Epidemiology and costs of herpes zoster: background data to estimate the impact of vaccination. Vaccine 2007; 25: 7598–7604.
26. Reynolds MA, Chaves SS, Harpaz R, Lopez AS, Seward JF. The impact of the varicella vaccination program on herpes zoster epidemiology in the United States: a review. J Infect Dis 2008; 197 Suppl 2: S224–S227.
27. Yih WK, Brooks DR, Lett SM, Jumaan AO, Zhang Z, Clements KM, et al. The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998–2003. BMC Public Health 2005; 5: 68.
28. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352: 2271–2284.
29. Rothberg MB, Virapongse A, Smith KJ. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Clin Infect Dis 2007; 44: 1280–1288.