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A population based study of the epidemiology of Herpes Zoster and its complications

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Summary *Objectives:* To assess the incidence of Herpes Zoster (HZ) and its complications in the Israeli general population and specifically in immune-compromised individuals, and to identify risk factors for developing HZ and post-herpetic neuralgia (PHN).
Methods: A retrospective database search for newly diagnosed cases of HZ and of PHN during 2006—2010 was conducted using the comprehensive longitudinal database of Maccabi Health Services. Cox-proportional hazards models were used to assess associations between risk factors and HZ and PHN.
Results: During 2006—2010 there were 28,977 newly diagnosed cases of HZ and 1508 newly diagnosed cases of PHN. Incidence density rate of HZ was 3.46 per 1000 person-years in the total population and 12.8 per 1000 person-years in immune-compromised patients. HZ and PHN incidence increased sharply with age. 12.4% and 3.1% of elderly HZ patients (≥65 years) developed PHN or ophthalmic complications, respectively. In multivariable analyses, HZ and PHN were associated with female sex, higher socioeconomic status, diabetes mellitus, cancer history, and HIV treatment.
Conclusions: Extrapolating to the entire Israeli population, we estimate over 24,000 new cases of HZ and 1250 new cases of PHN each year. Cost-effectiveness analysis should be performed to determine the threshold age for vaccination against HZ.

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Introduction

Herpes Zoster (shingles) is caused by varicella-zoster virus (VZV) reactivation, often several decades after the initial infection, and is characterized by painful dermatological symptoms. According to previous studies from the UK, Canada, and the USA the lifetime risk of developing HZ is 20%—30%.[1,2] Incidence increases markedly with age and is higher among patients with neoplastic diseases (especially lymphoproliferative cancers), organ-transplant recipients, and in those receiving immunosuppressive drugs, due to impaired cell-mediated immunity in these patients. The most common complication of HZ is post-herpetic neuralgia (PHN), a persistent pain that negatively affects the patient's quality of life and ability to function.[3] Precise definitions of PHN vary, but most authors use persistent pain for 1—3 months after the outbreak of the HZ rash.[4—7]

HZ vaccine has been shown to substantially reduce the risk of HZ and subsequent PHN in immune-competent elderly subjects.[8] The vaccine is licensed for use in the USA since 2006 and recommended in persons aged 60 years or above with no contraindications, such as primary or acquired immunodeficiency.[9] Despite lack of updated local data regarding the epidemiology of HZ, an advisory committee to the Israeli Ministry of Health has recently recommended immunization for elderly citizens. We undertook the present study to evaluate the incidence of HZ and its complications in the Israeli general population and among specific high-risk groups, as well as to assess the proportion of under-diagnosed HZ cases in the community. In recent years, use of biological immune-suppressants in Israel has increased due to inclusion of several new indications in the Israeli basket of health services.[10,11] Therefore we divided the analyses into two different time-periods: Incidence rates of HZ and PHN in the general population were derived for the years 2006—2010, whereas high-risk populations and complications other than PHN were studied during 2010.

Patients and methods

Data source and case definition

The present retrospective cohort analysis was conducted using the comprehensive longitudinal database of Maccabi Healthcare Services (MHS), the second largest health maintenance organization (HMO) in Israel, covering approximately 2 million individuals, or 25% of the total Israeli population. Since 1995, all Israeli citizens are universally covered under the 1994 National Healthcare Insurance Act that provides a comprehensive basket of services through four national HMOs. The age and sex distribution of MHS enrollees is comparable to the Israeli population distribution.[12] MHS' computerized database has been described previously.[13] Briefly, this database is a central data repository, retaining historical records of patient demographic data and clinical data, as well as laboratory results, hospitalizations, visits to specialists, dispensed medications, imaging tests, nursing, physiotherapy and other treatments. All MHS caregivers use a central computerized medical record.Using the individual's unique national identity number, these data can be identified to the level of the individual member. The study protocol was approved by the institutional review board of MHS.

Cases of HZ and of PHN were identified through a search of the database for *International Classification of Diseases*, 9th revision code of HZ (ICD 9 code, 053) and for relevant internal MHS codes from all general hospitals in Israel and from the community. We previously described the validity of a similar case finding method in 73 randomly selected HZ patients of whom 61 had supporting clinical evidence (including free text) in their medical records giving a predictive value of 84% (95% CI: 78%—93%).[13]

Epidemiology of HZ and PHN during 2006—2010

Cases of HZ were identified for the period of January 1, 2006 through September 30, 2010. To prevent capture of follow-up visits of previous HZ episodes, at least one year of enrollment in MHS was required before entry to the study. Recurrent cases were counted if they occurred one year or more after a previous visit accounted for HZ. Incident cases of PHN were identified for the period of January 1, 2006 through December 31, 2010 (to ensure capture of PHN up to 3 months after HZ). Annual age-specific incidence density rates (IDRs) of HZ and the proportion of patients subsequently developing PHN were calculated for the period of 2006—2010.

Assessment of under-diagnosed HZ

Diagnoses of PHN appeared in some medical records with no previous diagnosis of HZ, indicating that these patients did not seek medical care for their HZ episode. The proportion of such PHN cases out of all cases of PHN was used to estimate the proportion of undiagnosed HZ cases. Assuming that undiagnosed HZ cases had the same rate of PHN as diagnosed HZ patients for each age group, we then estimated the true IDRs of HZ.

Complications and high-risk patients during 2010

Clinical data on complications other than PHN were abstracted for HZ patients diagnosed between January and September 2010 using ICD9 codes. These complications included encephalitis, nerve palsies, myelitis, pneumonitis, otitis externa, ophthalmic complications, delayed contralateral hemiparesis, and hepatitis, and were considered complications of HZ if they were coded as HZ complications (sub hierarchy of ICD code 053), or if diagnosed 7 days before or up to 45 days after diagnosis of HZ. Delayed contralateral hemiparesis was followed for 180 days after diagnosis of an ophthalmic complication.

Analysis of HZ epidemiology among immunocompromised patients included identification of new cases of HZ between January and September 2010 and follow-up for PHN from January to December 31 2010. The immunocompromised patient group included: 1) patients who purchased at least two prescriptions of immunosuppressants or three prescriptions of corticosteroids in the half year of July—December 2009, 2) cancer patients receiving chemotherapy or radiotherapy who began their last treatment

during this period, 3) patients receiving anti-HIV drugs in 2009, and 4) patients who underwent a solid organ transplantation at any time, or who underwent a bone-marrow transplantation during 2009.

Finally, risk factors for HZ and for PHN were assessed. Data obtained for MHS members aged 25 or up included date of birth, sex, and history of cancer, diabetes mellitus (DM), and transplantations, as well as therapy for acquired immune deficiency syndrome (AIDS) or treatment with TNF-α blockers (i.e. at least one prescription in 2010). Data also included socioeconomic status (SES), categorized into tertiles according to the poverty index of the member's enumeration area, as defined by 1995 national census. The poverty index is based on several parameters including household income, educational qualifications, crowding, material conditions and car ownership.[14] DM patients were identified by using the MHS computerized diabetes mellitus patient registry.[15] Information on cancer history was provided by the Israel National Cancer Registry (INCR), which has collected information of diagnosed cancer cases from all medical institutions in Israel since 1960.

Hazard ratios and 95% confidence intervals were derived using Cox-proportional hazards (PH) regression for the association of baseline risk factors and study outcomes, namely incident HZ and PHN cases. PH assumptions were assessed visually by examining the log—log survival plots for each variable adjusted for the other covariates. Due to violation of the PH assumption for age, the final model was carried out separately for persons aged 25—84 and for those aged $\geq$85 years. SPSS version 19 was used in all analyses.

Results

Epidemiology of HZ and PHN during 2006—2010

During the study period there were 28,977 newly diagnosed cases of HZ and 1508 newly diagnosed cases of PHN among MHS members (Table 1). The IDR of HZ was 3.46 per 1000 person-years with a sharp increase with age, ranging from 2 per 1000 person-years among children and young adults to 10 per 1000 person-years among the elderly ($\geq$65 years of age). There was little variation in the annual IDR of HZ during the study period (Fig. 1). The mean age at diagnosis increased linearly from 43.3 years in 2006 to 46.1 years in 2010 (p-for linear trend $<$0.001) whereas the entire cohort aged by 14 months in this time interval. Recurrence rate of HZ was 2.9% during the study period, with a median time of 23.1 months between episodes. Overall 5.2% of HZ patients in 2006—2010 developed PHN, 2.0% in of the 25—44 age group and 12.4% of the elderly HZ patients. The mean time interval between the first reported diagnosis of HZ and reported diagnosis of PHN was 33 days, with a median of 17 days.

Assessment of under-diagnosed HZ

In 281 cases of PHN (18.9%) there was no documentation of HZ prior to the diagnosis of PHN. Thus we estimated the overall true IDR of HZ to be 4.65 per 1000 person-years and among the elderly 12.11 per 1000 person-years (Table 1).

Table 1 Age-specific incidence density rates of Herpes Zoster and proportion of patients developing post-herpetic neuralgia, Maccabi Healthcare Services, 2006—2010.

		Herpes Zoster					Post-herpetic neuralgia		
Age years	n	Follow-up years, mean	Cases	IDR per 1000 person-years	Male-to-female ratio	Estimated true IDR per 1000 person-years[a]	Proportion with PHN % (n)	PHN male-to-female ratio	Proportion of PHN cases without HZ visit % (n)
0—14	636,263	3.86 (1.41)	4694	1.91	1:1.12	2.39	0.11 (5)	1:0.63	20.0 (1)
15—24	264,831	4.20 (1.11)	2223	2.00	1:1.03	3.98	0.72 (16)	1:0.96	50.0 (8)
25—34	291,314	4.21 (1.22)	2875	2.35	1:0.97	3.03	1.81 (52)	1:0.82	23.1 (12)
35—44	309,827	4.35 (1.08)	3532	2.62	1:1.00	3.88	2.24 (79)	1:0.96	32.9 (26)
45—54	213,483	4.41 (1.00)	4182	4.44	1:1.45	5.79	4.95 (207)	1:0.75	24.1 (50)
55—64	159,690	4.39 (1.01)	5247	7.48	1:1.37	9.14	6.75 (354)	1:1.10	19.2 (68)
65—74	83,511	4.25 (1.17)	3633	10.23	1:1.20	11.77	11.56 (420)	1:1.09	14.5 (61)
75—84	45,380	4.02 (1.34)	2092	11.45	1:1.06	13.25	13.24 (277)	1:1.25	15.2 (42)
85+	16,410	3.39 (1.61)	499	8.97	1:0.89	10.51	15.43 (77)	1:0.77	16.9 (13)
Total	2,020,709	4.15 (1.24)	28,977	3.46	1:1.21	4.56	5.20 (1508)	1:1.13	18.9 (281)

[a] See text for details.

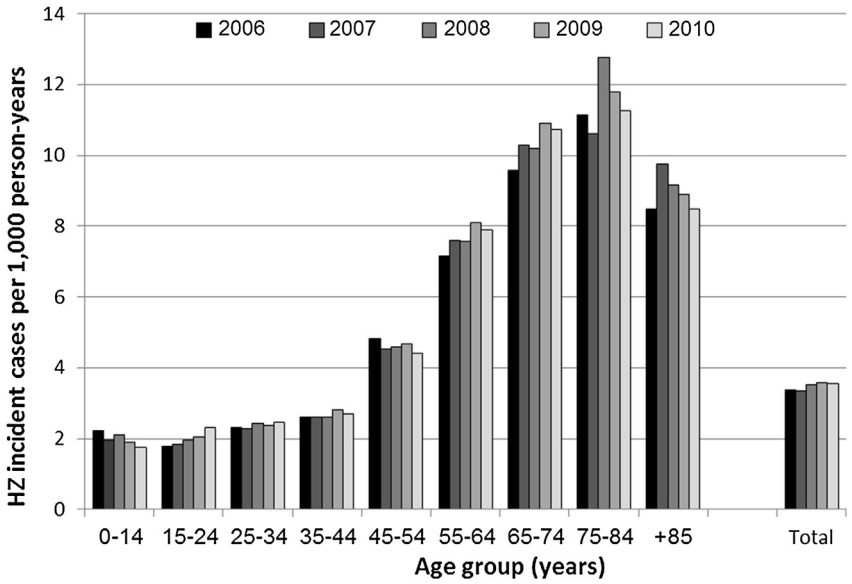

Figure 1 Annual age-specific incidence density rates of Herpes Zoster, Maccabi Health Services 2006—2010 ($N = 2{,}020{,}709$).

Complications and high-risk patients during 2010

In addition to PHN, other common complications of HZ included ophthalmic disease and otitis externa, occurring in 25.01 and 5.71 per 1000 HZ patients, respectively (Table 2). There were no reported cases of pneumonitis. Among 23,420 immunocompromised patients followed during 2010, there were 207 cases of HZ (Table 3), yielding IDRs of 12.8 and 14.6 per 1000 person-years in patients aged ≥25 and in the elderly, respectively. PHN was diagnosed in 11.6% and 17.0% in immunocompromised patients aged ≥25 and in the elderly, respectively.

Table 2 Cumulative incidence of selected HZ complications[a] per 1000 patients aged 25 years and up, Maccabi Healthcare Services Jan—Sep 2010.

		Cumulative incidence of HZ complications[a] per 1000 HZ patients						
Age years	No. of HZ patients	Hepatitis	Ophthalmic complications	Otitis externa	DCH	Myelitis	Nerve palsies	Encephalitis
25—44	1045	0.96	24.88	4.78	0	0	0.96	0.96
45—64	1616	0.62	21.66	6.19	0	0.62	4.33	0
65—84	939	1.06	27.69	6.39	1.06	0.00	2.13	0
85+	78	0	64.10	0	0	0	0	0
Total	3678	0.82	25.01	5.71	0.27	0.27	2.72	0.27

DCH: delayed contralateral hemiparesis.
[a] Diagnosed 7 days before or up to 45 days after diagnosis of HZ. Delayed contralateral hemiparesis was followed for 180 days after diagnosis of an ophthalmic complication.

Table 3 Age-specific incidence density rates of HZ and proportion developing post-herpetic neuralgia in immunocompromised patients, Maccabi Healthcare Services, Jan—Sep 2010.

Age years	*n*	HZ incident cases	IDR per 1000 PY	Proportion developing PHN (n)
25—34	1604	4	3.37	0
35—44	3348	21	8.53	0
45—54	4304	27	8.56	7.4% (2)
55—64	5744	67	16.06	10.5% (7)
65—74	4577	54	16.35	16.7% (9)
75—84	3006	27	12.63	18.5% (5)
85+	837	7	12.04	14.3% (1)
Total	23,420	207	12.18	11.6% (24)

In a multivariate Cox-regression analysis in the 25—84 age range, in addition to age, HZ and PHN were associated with female sex, higher SES, DM, history of cancer and receiving treatment for HIV (Table 4). Notably, high HRs for PHN were observed for ages 65 and up (HRs = 20.9—19.5) and for persons treated for HIV (HR = 15.5). Use of anti-TNFalpha medication increased the risk of HZ and of PHN, but the latter association was not statistically significant. History of transplantation was not an independent risk factor for HZ or for PHN, and therefore was not included in the model. Among persons aged ≥85 up, history of cancer increased the risk for HZ, with HR = 3.57 (95% CI:0.87—14.66) for a history of 1 year and HR = 1.77 (95% CI:0.98—3.19) for a history of 5 years or more.

Discussion

The results of this population based cohort indicate a substantial annual risk of HZ of about 4.5 per 1000, with one in twenty HZ patients further developing PHN. Similar to previous studies, we found a strong association between age and occurrence of HZ[2,4—7,16—20] and of PHN.[4—7,20] Our analysis provides further evidence of the importance of well-known HZ risk factors such as female sex,[6,7,16,17,21,22] diabetes,[13,20,23] and immunocompromised conditions.[7,16,17,20,23—26]

The overall IDRs of HZ in this current study are in the higher range of those reported for other developed countries which range between 1.2 and 5.5 per 1000 per year.[17,22] Similarly, our estimates of age-specific HZ risk among the elderly (12.11 and 12.61 per 1000 among the aged 65 years and 75 years or more, respectively) are in the higher range of previously reported estimates.[1,2,4,6,7,16—19] The relatively high HZ risk calculated in this study can be explained by our automated capturing of community cases and the universal access to healthcare services in Israel. According to a Ministry of Health report, the average number of annual physician visits among elderly Israelis is 15,[27] one of the highest in the world. This may explain the relatively low proportion of underreported HZ cases in this age group. Due to the high proportion of cases captured, we believe that our cohort may have consisted of more mild HZ cases compared to previous similar studies. This, in turn, may explain the comparatively low proportion of HZ patients diagnosed with PHN in this study (5.2% overall and 12.4% among the elderly), as compared to 6—18% in adults and 14%—29% in Netherlands,[4,19] the UK,[6] and the US.[5] PHN has been shown to occur more often among severe HZ cases.[28] Another possible explanation for the somewhat lower occurrence of PHN in the current study is that since the coding was not specifically designated for research purposes, the physicians may have attributed less importance to sub-types of diagnosis and may have used the more general HZ code for diagnosis. HZ ophthalmicus was also diagnosed less often than in a previous report,[4] where screening of text-data within medical records was used.

Some studies have shown a major increase in HZ rates over time with[29] or without[21,30] association to the introduction of childhood VZV immunization. Our time-trend analysis suggested only minor changes occurring before and after 2008, the year when the VZV vaccine was introduced to the universal childhood immunization program in Israel.

Studies in various immunocompromised patient populations have shown increased risk for HZ and PHN. For example, SLE patients experienced an incidence of 6.4 HZ events/1000 person-years, mostly due to concomitant use of corticosteroids and immunosuppressants.[25] According to one study, patients with Crohn's disease who received

Table 4 Hazard ratios and 95% confidence intervals for the association of incident cases of HZ and of post-herpetic neuralgia, Maccabi Healthcare Services 2010.

			Herpes Zoster		Post-herpetic neuralgia	
Risk factor	Sub group	No. of persons	Incident cases	Hazard ratios (95% CI)	Incident cases	Hazard ratios (95% CI)
Age (years)	25—34	248,479	449	1 (ref.)	11	1 (ref.)
	35—44	297,431	596	1.10 (0.98—1.25)	10	0.75 (0.32—1.78)
	45—54	207,558	675	1.77 (1.57—1.99)	36	3.80 (1.93—7.47)
	55—64	161,266	941	3.05 (2.72—3.42)	66	8.38 (4.41—15.93)
	65—74	77,838	613	3.95 (3.49—4.49)	84	20.90 (11.04—39.57)
	75—84	39,841	326	4.02 (3.47—4.66)	41	19.51 (9.89—38.48)
Sex	Female vs. males	539,670	2067	1.23 (1.15—1.31)	152	1.44 (1.12—1.86)
SES (tertiles)	High vs. other	278,664	1080	1.11 (1.03—1.19)	89	1.39 (1.07—1.81)
Cancer history	None	994,917	3284	1 (ref.)	214	1 (ref.)
	<1 year	3479	38	2.13 (1.54—2.93)	5	3.00 (1.23—7.30)
	1—5 years	16,665	143	1.58 (1.33—1.87)	17	1.91 (1.16—3.14)
	5+ years	17,352	135	1.37 (1.15—1.63)	12	1.17 (0.65—2.11)
Diabetes mellitus	Yes. vs. no	82,064	533	1.17 (1.06—1.29)	58	1.35 (0.99—1.83)
HIV treatment	Yes. vs. no	627	6	3.92 (1.76—8.73)	1	15.53 (2.17—111.21)
Anti-TNF-α	Yes. vs. no	1316	13	2.73 (1.58—4.70)	1	2.95 (0.41—21.06)
Transplantation history[a]	Yes. vs. no	409	2	1.03 (0.26—4.12)	0	NA

[a] Not included in final model.

monotherapy with steroids, immunosuppressants, or anti-TNF agents had a 70% higher risk for HZ. The relative risk for HZ in patients receiving more than one of these medications was 3.7. Similarly, in the current study, elderly immunocompromised patients were at 1.4-fold higher risk for both HZ and PHN. In the multivariate analysis, an HR of 3.88 was found for the risk of HZ in patients receiving anti-HIV therapy. Recent studies reported a 10-fold increased risk for HZ in HIV-positive persons compared to HIV-negative persons.[26,31]

DM, history of cancer and anti-TNF alpha treatments were also independently associated with an elevated risk for HZ as well as for subsequent PHN. DM patients have been shown to be more susceptible to infections than DM-free individuals,[32] as we have shown using the MHS database.[13] While Schmader et al.[33] did not detect an association between lifetime history of cancer and risk for HZ in the elderly, we have found that although the HZ risk declined with time since cancer diagnosis, it was still significant at least 5 years afterward. This may be explained by continuous immunosuppressive therapy in long-term cancer patients.

Additional independent HZ risk factors were female sex and higher socioeconomic status. Other studies also reported a higher incidence of HZ in females, with a relative risk in the range of 1.2—1.4.[6,7,17] In data from England, Wales and Canada[34] no association was found between socioeconomic status and risk for HZ.[17] A previous study in Israel showed higher anti-VZV vaccination rates in Israeli children with high versus low SES in the era prior to universal vaccination, i.e. before 2008.[35] This raises a case for further study to assess whether Israeli children of lower SES indeed had a higher incidence of VZV and if their family members experienced decreased rates of HZ, as suggested by some studies[36,37] but not all.[30,38]

To the best of our knowledge, the present study is one of the largest studies on the incidence of HZ and its complications in the general population as well as in high-risk patients. Other study strengths include the comprehensive and systematic data collection and high accessibility to MHS' healthcare services. Nevertheless, some limitations of the study should be considered. Case definition was based on physician consultations and hospital records, and thus data on undiagnosed or misdiagnosed cases and complications were unavailable. Specifically, ascertainment of PHN cases depended on physicians' definition of PHN and was subject to the inability to differentiate between the duration of PHN and degrees of pain severity. The mean time interval between HZ and PHN diagnoses suggests that physicians tended to use a 1-month definition.

Extrapolating the incidence of HZ and PHN to the entire Israeli population, we estimate over 24,000 new cases of HZ and 1250 new cases of PHN each year. A cost-effectiveness analysis, taking into account long-term effects on the quality of life of PHN patients, should be carried out to determine the threshold age for vaccination against HZ. This analysis should take into account the increasing proportion of the aging population both in the Western and the non-Western world,[39] increasing use of immunosuppressive therapies, and trends over time in the epidemiology of the disease.

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