The Incidence of Herpes Zoster in a United States Administrative Database

Ralph P. Insinga, PhD,¹ Robbin F. Itzler, PhD,¹ James M. Pellissier, PhD,¹
Patricia Saddier, MD, PhD,² Alexander A. Nikas, MS²

¹Department of Health Economic Statistics; ²Department of Epidemiology,
Merck Research Laboratories, Blue Bell, Pa, USA.

BACKGROUND: Few recent studies have reported data on the incidence of herpes zoster (HZ) in U.S. general clinical practice.

OBJECTIVE: To estimate the age- and sex-specific incidence of HZ among U.S. health plan enrollees.

DESIGN: Data for the years 2000 to 2001 were obtained from the Medstat MarketScan database, containing health insurance enrollment and claims data from over 4 million U.S. individuals. Incident HZ cases were identified through HZ diagnosis codes on health care claims. The burden of HZ among high-risk individuals with recent care for cancer, HIV, or transplantation was examined in sub-analyses. Overall incidence rates were age- and sex-adjusted to the 2000 U.S. population.

PARTICIPANTS: MarketScan U.S. health plan enrollees of all ages.

MEASUREMENTS AND MAIN RESULTS: We identified 9,152 incident cases of HZ (3.2 per 1,000 person-years) (95% confidence interval [CI], 3.1 to 3.2 per 1,000). Annual HZ rates per 1,000 person-years were higher among females (3.8) than males (2.6) ($P < .0001$). HZ rates rose sharply with age, and were highest among individuals over age 80 (10.9 per 1,000 person-years) (95% CI, 10.2 to 11.6). The incidence of HZ per 1,000 person-years among patients with evidence of recent care for transplantation, HIV infection, or cancer (10.3) was greater than for individuals without recent care for these conditions (3.0) ($P < .0001$).

CONCLUSIONS: The overall incidence of HZ reported in the present study was found to be similar to rates observed in U.S. analyses conducted 10 to 20 years earlier, after age- and sex-standardizing estimates from all studies to the 2000 U.S. population. The higher rate of HZ in females compared with males contrasts with prior U.S. studies.

KEY WORDS: zoster; shingles; incidence; cancer, HIV.

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Herpes zoster (HZ), or shingles, is a cutaneous disease caused by the reactivation of latent varicella-zoster virus (VZV) dormant in cranial nerve or dorsal root ganglia.¹ Herpes zoster arises years or decades following primary infection with VZV, which usually results in clinical varicella (chicken pox).¹ Herpes zoster cases typically present with a characteristic unilateral, localized, vesicular eruption accompanied by pain in the affected dermatome,^{2,3} and patients may also experience insomnia, anxiety, and general malaise.^{1,3} The vesicular eruption is often preceded by localized prodromal pain,^{4,5} sometimes accompanied by headache, malaise, and disrupted sleep.³

The acute vesicular eruption typically heals within 2 to 3 weeks,⁶ but chronic pain (postherpetic neuralgia [PHN]) can persist for months or years thereafter^{7,8} and may be intractable

and disabling in spite of pharmacologic therapy.^{6,9} The risk of developing HZ has been observed to increase sharply with age,^{10,11} and long-lasting zoster-associated pain tends to be more frequent and severe in older individuals.^{5,12} Ophthalmic complications occur in approximately 5% to 10% of patients,^{13,14} and HZ may also be associated with cranial and peripheral nerve palsies, such as Ramsay Hunt Syndrome.¹⁵ More rarely, and primarily in immunocompromised subjects, HZ-related complications of visceral dissemination, myelitis, and encephalitis can occur.¹⁵ HZ is responsible for a widespread health burden and may occur in up to 20% of individuals during their lifetimes.¹⁶

Early reports of the incidence of HZ were derived from physician practice populations in the UK,^{17,18} and several recent international studies have also described the incidence of HZ.^{11,13,19–21} However, only 2 U.S. studies, conducted in a New England HMO,¹⁰ and a small New Hampshire solo practice,²² have reported data since 1960 on the incidence of HZ in U.S. general clinical practice. Current data on the incidence of HZ are needed to inform policy evaluations of emerging therapeutic and preventive agents targeting HZ, such as vaccines.²³ Individuals with conditions and treatments resulting in a marked decrease in cellular immunity are at increased risk for developing HZ.^{1,24} While previous U.S. studies have reported a high incidence of HZ among immunocompromised individuals, most have been restricted to specialized groups of patients (e.g., hemophiliacs infected with HIV),^{25–27} and relatively few data are available on the incidence of HZ among general populations of patients with conditions/treatments that may result in immunosuppression.

Using a large health care claims database comprised of individuals from all 50 states, the present study estimates the age- and sex-specific incidence of HZ episodes among U.S. health plan enrollees. In addition, the burden of HZ is described among patients at high risk for the development of HZ who have evidence of recent care for cancer, HIV infection, or transplantation (solid organ, bone marrow, or stem cell), conditions/treatments that result in varying degrees of immunosuppression.

METHODS

Data were derived from the Medstat MarketScan database (Copyright 2001, The Medstat Group, Inc., All Rights Reserved.), containing health insurance enrollment data from ~ 4 million privately insured U.S. individuals of all ages, along with records of inpatient, outpatient, emergency room, and pharmacy health insurance claims. Consistent with prior analyses, incident cases of HZ were identified through the appearance of an International Classification of Disease, Ninth

All authors are employed by Merck Research Laboratories.

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Address correspondence and requests for reprints to: Dr. Insinga, PhD, 10 Sentry Parkway, BL 2-3, Blue Bell, PA 19422 (e-mail: ralph_isinga@merck.com).

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Revision (ICD-9) principal or secondary diagnosis code for HZ (ICD-9 codes 053.0-053.11, 053.19-053.9)¹⁰ on a health care claim. To qualify as an incident case, individuals must have had an HZ diagnosis code on a claim during the 12-month period from July 1, 2000 to June 30, 2001, without evidence of a previous diagnosis for HZ on a claim for at least 180 days prior to the diagnosis in question. This 180-day period is consistent with that used in previous analyses of HZ incidence,¹⁰ and is designed to distinguish the start of a new HZ episode from follow-up care relating to a prior HZ diagnosis. Enrollees with fewer than 180 days of continuous health plan enrollment prior to the start of the ascertainment period for incidence were excluded from the analysis ($n=1,527,484$ excluded). Exclusions because of insufficient enrollment resulted from the entry and exit of health plans from the MarketScan database during the period of observation, and enrollee insurance turnover. The frequency of health care claims with a diagnosis code for HZ during the analysis period did not differ between all MarketScan enrollees and the sample eligible for analysis (6.3 vs 6.2 HZ claims per 1,000 person-years). Consistent with prior analyses,¹⁰ individuals with episodes first denoted by a diagnosis code for PHN (ICD-9 codes 053.12, 053.13) were not included among the group of incident cases (0.9% of all individuals with HZ or PHN codes), because of the increased potential for these cases to represent sporadic long-term follow-up for a prior HZ episode.

Sub-analyses were conducted to examine HZ incidence among individuals with evidence of recent care for cancer, HIV infection, or transplantation. These conditions and treatments may result in immunosuppression, which has been found to increase the risk of developing HZ.^{1,24,28} Receipt of recent care for cancer, HIV infection, or transplantation was defined by the presence on a health care claim of diagnosis, procedure, or drug codes indicative of these conditions/treatments during the 180 days prior to an HZ diagnosis as described in Table 1. Care for cancer reflected health care encounters for malignancy (excluding nonmelanoma skin cancers) and chemotherapy. HIV care included HIV-related health care encounters, in addition to prescription fills for antiretroviral and other drugs used in the treatment of HIV. Care for transplantation reflected health care encounters for solid organ, bone marrow, or stem cell transplantation.

Incidence rates were estimated by dividing the number of incident HZ cases observed during the period of observation, by the number of years of person-time contributed by individuals in the MarketScan population. Standard errors for point

estimates of incidence were calculated through age- and sex-stratified regression analyses utilizing a negative binomial distribution, and used to estimate 95% confidence intervals (CI). *P* values for differences in HZ rates across age and gender categories were derived through negative binomial regression.²⁹ To enhance external generalizability, overall incidence rates by age were sex adjusted to the 2000 U.S. population,³⁰ with age and sex adjustment to this standard for estimates reported across all enrollees. Adjustment of incidence rates across all age and sex strata was performed by weighting MarketScan data for individuals within each age and sex strata by $(n_{ij(U.S.)}/N_{(U.S.)} \times N_{(MarketScan)})/n_{ij(MarketScan)})$, where *N* represents the total population person-years within the U.S. and MarketScan populations and *n_{ij}* reflects the number of person-years observed within the respective age (*i*) and sex (*j*) strata of interest. Analogous methods were used in adjustments within sex and age groupings. Data were unavailable for adjusting for additional demographic variables such as income and education.

RESULTS

Demographic characteristics for the 2000 to 2001 MarketScan population included in the analysis are presented in Table 2, alongside those for the 2000 U.S. population. The 2,808,160 MarketScan individuals eligible for analysis covered a full range of ages and were drawn from all geographic regions of the U.S., although the proportion residing in the Midwest was somewhat higher (31% vs 23%) and in the West somewhat lower (14% vs 23%) than that observed in the U.S. general population.³¹ Although sex frequencies were similar, MarketScan enrollees tended to be slightly older than individuals in the U.S. general population. By plan type, 77.3% of MarketScan enrollees were in fee-for-service health plans, compared with 22.7% in capitated arrangements.

A total of 9,152 incident cases of HZ were observed during the 12-month study period. Following age and sex adjustment to the 2000 U.S. population, 59.9% of HZ cases were estimated to occur among females, compared with 40.1% among males. As seen in Figure 1, HZ was observed among patients of all ages, with patients most heavily concentrated between the ages of 50 and 79.

The age- and sex-specific incidence of HZ is reported in Table 3. Across all ages, the overall age- and sex-adjusted incidence of HZ was 3.2 per 1,000 person-years (95% CI, 3.1 to 3.2). The corresponding crude incidence rate was 3.8 per

Table 1. Administrative Codes Used to Identify Recent Care for Cancer, HIV, and Transplantation

Condition/Treatment	Code Type*	Codes
Cancer		
Health care encounters	ICD-9 diagnosis	140-172, 174-208, 235-239
Chemotherapy/anti-neoplastic agents	ICD-9 procedure	99.25, 99.28
HIV		
Health care encounters	ICD-9 diagnosis	042-044, 079.53, V08
Drugs prescribed for HIV	NDC	†
Transplantation†		
Health care encounters	ICD-9 diagnosis	V42.0-V42.2, V42.6-V42.9, 996.80-996.89
Transplant procedures	ICD-9 procedure	33.5, 37.5, 41.09, 41.94, 50.5, 52.8, 55.6

*ICD-9, International Classification of Disease, Ninth Revision; NDC, National Drug Code.

†Because of the large number of drugs selected for identifying HIV ($n=21$) cases, drug names are not listed individually (list available upon request).

‡Solid organ, bone marrow, or stem cell transplantation.

Table 2. Demographic Characteristics of MarketScan and U.S. Populations

Characteristic	2000 to 2001 MarketScan Population N (%)	2000 U.S. Population N (%)
All	2,808,160 (100.0)	281,421,906 (100.0)
Age		
0 to 14	450,134 (16.0)	60,253,375 (21.4)
15 to 29	456,571 (16.3)	58,565,227 (20.8)
30 to 39	365,173 (13.0)	43,217,052 (15.4)
40 to 49	480,750 (17.1)	42,534,267 (15.1)
50 to 59	469,498 (16.7)	31,054,785 (11.0)
60 to 69	294,658 (10.5)	20,338,992 (7.2)
70 to 79	197,827 (7.0)	16,273,254 (5.8)
≥ 80	93,549 (3.3)	9,184,954 (3.3)
Sex		
Male	1,331,347 (47.4)	138,053,563 (49.1)
Female	1,476,523 (52.6)	143,368,343 (50.9)
Region*		
Northeast	475,366 (16.9)	53,470,162 (19.0)
South	1,077,459 (38.4)	100,186,199 (35.6)
Midwest	871,814 (31.1)	64,445,616 (22.9)
West	380,765 (13.6)	63,319,929 (22.5)

*Data on region missing for 2,756 MarketScan enrollees.

1,000 person-years. The rate of HZ was higher among females (3.8 per 1,000 person-years) (95% CI, 3.7 to 3.9) than among males (2.6 per 1,000 person-years) (95% CI, 2.5 to 2.7), and remained so after controlling for age and recent care for cancer, HIV infection, or transplantation through regression ($P < .0001$). The incidence of HZ increased with age, with the highest rates observed among enrollees over age 80 (10.9 per 1,000 person-years) (95% CI, 10.2 to 11.6).

Little variation was observed in the overall incidence of HZ by U.S. region, with age- and sex-standardized rates of 2.9, 3.2, 3.3, and 3.3 per 1,000 person-years, respectively, among individuals residing in the Northeast, South, Midwest, and West. Across all incident episodes, 91.3% of initial HZ diagnoses were observed to have been made in physician offices, compared with 2.8% in emergency rooms, 1.8% during inpatient hospital admissions, and 3.9% in other settings (e.g., long-term care facilities).

The incidence of HZ among individuals with and without recent care for cancer, HIV infection, or transplantation is reported in Table 4. Among patients with recent care for cancer,

FIGURE 1. Distribution of herpes zoster cases in the MarketScan population ($n=9,152$) by age group. Exact percentages are listed above each bar and are age- and sex-adjusted to the 2000 U.S. population.

HIV infection, or transplantation, the overall incidence of HZ was 10.3 per 1,000 person-years (95% CI, 9.7 to 11.0), compared with a rate of 3.0 per 1,000 person-years (95% CI, 2.9 to 3.0) among patients lacking evidence of recent care for these conditions/treatments. Recent care for cancer, HIV infection, or transplantation was associated with a higher rate of HZ regardless of age or sex ($P < .0001$). However, the degree to which evidence of these conditions/treatments was associated with a higher rate of HZ incidence, as expressed by rate ratios, was lower among patients over age 50 (1.8) than among younger patients (3.6) ($P < .0001$).

Overall, 8.7% of HZ patients had evidence of recent care for cancer, HIV infection, or transplantation. The proportion of HZ patients with recent care for these conditions/treatments was low among both individuals younger (4.3%) and older (11.7%) than age 50.

DISCUSSION

Since 1960, only 2 U.S. studies, conducted in the Harvard Community Health Plan (HCHP) HMO¹⁰ and a small New Hampshire solo practice,²² have reported data on the incidence of HZ in U.S. general clinical practice. Using 1990 to

Table 3. Incidence of Herpes Zoster Per 1,000 Person-Years By Age and Sex

Age	Males			Females			Both Sexes		
	Person-Years	Cases	Rate per 1,000 Person-Years (95% CI)	Person-Years	Cases	Rate per 1,000 Person-Years (95% CI)	Person-Years	Cases	Rate per 1,000 Person-Years* (95% CI)
0 to 14	186,291	166	0.9 (0.8, 1.0)	177,660	231	1.3 (1.1, 1.5)	363,951	397	1.1 (1.0, 1.2)
15 to 29	187,660	219	1.2 (1.0, 1.3)	189,916	308	1.6 (1.4, 1.8)	377,576	527	1.4 (1.3, 1.5)
30 to 39	138,007	264	1.9 (1.7, 2.2)	161,668	336	2.1 (1.9, 2.3)	299,675	600	2.0 (1.8, 2.2)
40 to 49	190,653	473	2.5 (2.3, 2.8)	228,677	740	3.3 (3.0, 3.5)	419,330	1,213	2.9 (2.7, 3.0)
50 to 59	199,300	749	3.8 (3.5, 4.0)	229,801	1,240	5.4 (5.1, 5.7)	429,101	1,989	4.6 (4.4, 4.8)
60 to 69	122,101	741	6.1 (5.6, 6.5)	135,162	1,037	7.7 (7.2, 8.1)	257,263	1,778	6.9 (6.6, 7.2)
70 to 79	82,317	699	8.5 (7.9, 9.1)	96,958	993	10.3 (9.6, 10.9)	179,275	1,692	9.5 (9.0, 9.9)
≥ 80	33,776	319	9.4 (8.4, 10.5)	54,450	637	11.7 (10.8, 12.6)	88,226	956	10.9 (10.2, 11.6)
Overall†	1,140,105	3,630	2.6 (2.5, 2.7)	1,274,292	5,522	3.8 (3.7, 3.9)	2,414,397	9,152	3.2 (3.1, 3.2)

*Age-specific rates for both sexes are sex-adjusted to the 2000 U.S. population.

†Overall rates for males and females are age-adjusted to the 2000 U.S. population. Overall rate for both sexes is age- and sex-adjusted to the 2000 U.S. population.

CI, confidence interval.

Table 4. Incidence and Concentration of Herpes Zoster (HZ) Among Patients With and Without Recent Care For Cancer, HIV Infection, or Transplantation*

Patient Group	Person-Years	Cases	Rate per 1,000 Person-Years [†] (95% CI)	% of HZ Patients [†]
All ages				
Cancer, HIV, or transplantation	82,847	865	10.3 (9.7, 11.0)	8.7
No cancer, HIV, or transplantation	2,331,550	8,287	3.0 (2.9, 3.0)	91.3
Overall	2,414,397	9,152	3.2 (3.1, 3.2)	100.0
Age 0 to 49				
Cancer, HIV, or transplantation	20,001	127	6.2 (5.2, 7.4)	4.3
No cancer, HIV, or transplantation	1,440,531	2,610	1.7 (1.6, 1.8)	95.7
Overall	1,460,532	2,737	1.7 (1.7, 1.8)	100.0
Age ≥ 50				
Cancer, HIV, or transplantation	62,845	738	12.2 (11.4, 13.1)	11.7
No cancer, HIV, or transplantation	891,020	5,677	6.6 (6.5, 6.8)	88.3
Overall	953,865	6,415	7.0 (6.8, 7.2)	100.0

*As measured by the presence or absence of a diagnosis, procedure, or drug code for cancer, HIV infection, or transplantation (solid organ, bone marrow, or stem cell) during the 180 days prior to a physician diagnosis of herpes zoster.

[†]Overall rates and percentages age- and sex-adjusted to the 2000 U.S. population.

1992 data from automated medical records, a crude annual incidence of HZ episodes of 2.1 per 1,000 person-years was reported in the HCHP analysis.¹⁰ However, when incidence rates from the HCHP study were age- and sex-adjusted to the 2000 U.S. population (our estimations), the annual incidence of HZ (3.3 per 1,000 person-years) was found to very similar to that observed in the MarketScan analyses (3.2 per 1,000 person-years). A crude HZ incidence rate of 3.3 per 1,000, and age- and sex-adjusted rate (our estimations) of 3.7 per 1,000, were estimated based on patients seen for HZ within the New Hampshire solo practice between 1983 and 1992; although population denominators were defined with less certainty in that analysis.²² The age- and sex-adjusted incidence rates reported for the U.S. are similar to those observed internationally for France (3.2 per 1,000 person-years),²⁰ the Netherlands (3.4 per 1,000 person-years),¹³ Canada (3.5 per 1,000 person-years),¹⁹ and the United Kingdom (U.K.) (3.8 per 1,000 person-years).¹⁹

Previous estimates of the annual number of incident cases of HZ within the U.S. have utilized incidence rates similar to the unadjusted rate from the HCHP study.^{1,5,10} This has resulted in projections of an annual burden of HZ within the U.S. population of approximately 500,000 cases.^{1,5,10} However, when extrapolated to the general population,³⁰ the age- and sex-adjusted estimates of incidence from recent U.S. studies would translate to nearly 1,000,000 cases of HZ diagnosed in the U.S. each year, suggestive of a higher absolute burden of HZ within the U.S. population than that previously estimated.^{1,5,10}

Consistent with previous studies, the burden of HZ was substantially higher among the elderly than among younger individuals.^{10,13,19}

The incidence of HZ was higher among females than males within all age groups. This finding contrasts with prior U.S. studies, in which a similar incidence of HZ was observed across the sexes,^{10,32} but is consistent with results from a large U.K. study, utilizing data from 1994 to 2001, which found a 28% higher age standardized incidence of HZ among females compared to males.¹¹ Standardizing data for both sexes in the present analysis to the age distribution of the 2000 U.S. population³⁰ yielded a similar excess incidence for females compared with males of 33%. This figure was only slightly attenuated after controlling for recent care for condi-

tions and treatments which may result in immunosuppression (i.e., cancer, HIV infection, and transplantation).

The reasons underlying gender differences in HZ incidence remain unclear. Given that HZ diagnoses examined in the present study were reflective of health care encounters, the gender differential could be caused in part by differences in care-seeking behavior. It has also been posited that females may have a differing immune response than males to latent viral infection.¹¹ The finding of a higher HZ incidence among females has raised questions concerning the relative magnitude of importance of a purported association between repeated exposure to VZV and a reduced risk of HZ.^{11,33} Females typically have more direct contact with children than males, including children with varicella.^{34,35} A strong negative association between repeated exposure to VZV and subsequent HZ would lead one to expect a lower risk of HZ among females than among males, the opposite of the pattern observed in the present analysis. Further studies are needed to better determine the reasons for these gender differences.

There has been little prior investigation of geographic variability in the incidence of HZ within the U.S. In the present study, there was found to be little regional variation between the Northeast, Midwest, South, and West in the frequency of HZ.

The age- and sex-adjusted risk of developing HZ among individuals with recent care for cancer, HIV infection, or transplantation was observed to be significantly higher than among individuals without recent care for these conditions/treatments. Although aggregated incidence rates with respect to these conditions/treatments are reported in this study, it should be noted that there is likely to be considerable variation in the level of immunosuppression, and subsequent risk of HZ, within and across patient groups with evidence of recent care for cancer, HIV, or transplantation.

Overall, 9% of HZ patients had evidence of recent care for cancer, HIV infection, or transplantation, supporting the notion that the vast majority of patients developing HZ may not have a recent history of an immunosuppressive comorbid condition that would constitute an obvious risk factor for HZ. This finding is consistent with results observed previously in the HCHP study in which 11% of HZ patients were found to have had a diagnosis code for cancer or HIV within the 6 months prior to an HZ diagnosis.²¹

This study has several potential limitations. First, consistent with other population-based studies of HZ,^{10,11,32} disease incidence in the present analysis was based upon the observation of a health care encounter for HZ. It is possible that some individuals developing HZ may not seek medical care; however, the frequency with which this may occur is unknown.

Second, incident cases were identified based on the appearance of an ICD-9 diagnosis code for HZ on a health care claim. Thus, the validity of the results depends upon the accuracy of a physician-assigned diagnosis of HZ and the resultant diagnostic coding generated by a given encounter. Although misclassification between HZ and herpes simplex virus has been reported in the literature,^{36–38} the routine clinical diagnosis of HZ is generally regarded as reliable.¹ For instance, in prior studies, the presence of HZ was confirmed in >90% of physician-diagnosed cases based on expert review of clinical data,³⁶ and 100% of clinically diagnosed cases based on polymerase chain reaction (PCR) testing.³⁷ It is difficult to comprehensively assess the degree to which HZ may be categorically misdiagnosed as another condition; however, HZ was not found to be a common cause of unexplained unilateral pain,³⁹ with evidence that a modest proportion of HZ cases may be misdiagnosed as herpes simplex.³⁷ For the present study, it was not possible to compare diagnoses listed on healthcare claims with those found in the medical record. However, the overall incidence of HZ reported within the MarketScan population is quite similar to that reported in prior U.S. (following age and sex adjustment) and international studies utilizing electronic medical records.^{10,13,19}

Finally, the identification of individuals with recent care for cancer, HIV infection or transplantation was based upon the observation of diagnosis, procedure, and drug codes related to these conditions/treatments on a health care claim. Thus, the caveats noted previously with respect to the accuracy of administrative coding apply. In addition, the potential exists for missed cases of cancer or HIV infection, particularly if HZ patients harbor occult disease that is not diagnosed until after the HZ diagnosis. However, several studies have established that HZ is not a marker for occult malignancy, with a risk of cancer following an HZ diagnosis similar to that observed within the general population.^{40–42} Similarly, prior U.S. analyses have not found HZ to be a harbinger of previously undiagnosed HIV infection.^{43,44} The accuracy of administrative coding for identifying individuals with the conditions/treatments examined in this analysis is expected to be adequate, given their relative severity, as evidenced by previous studies that have generally found claims data to be sufficiently reliable for identifying individuals with cancer.^{45,46}

This paper has reported data from the largest and most geographically diverse U.S. study of HZ incidence to date. A higher incidence of HZ was observed among females than males and among individuals at older ages. Age- and sex-standardized results for overall HZ incidence from the present study were found to be comparable to rates from U.S. studies conducted 10 to 20 years earlier,^{10,22} and similar to those observed in Canada and Europe.^{11,13,19} Although the MarketScan population does not reflect a national random sample of the population, the majority of Americans (~70%) have private health insurance coverage similar to MarketScan enrollees.⁴⁷ Extrapolated to the U.S. general population, results from this analysis would suggest that nearly 1 million new cases of HZ

are diagnosed in the U.S. each year. It is hoped that emerging technologies will help to reduce this health burden.

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