MAJOR ARTICLE

Herpes Zoster Incidence Among Insured Persons in the United States, 1993–2006: Evaluation of Impact of Varicella Vaccination

Jessica Leung,[1] Rafael Harpaz,[1] Noelle-Angelique Molinari,[1] Aisha Jumaan,[1,2] and Fangjun Zhou[1]

[1]National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, [2]HPV Vaccines Project, Program for Appropriate Technology in Health (PATH), Seattle, Washington

Background. Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus and is often associated with substantial pain and disability. Baseline incidence of HZ prior to introduction of HZ vaccine is not well described, and it is unclear whether introduction of the varicella vaccination program in 1995 has altered the epidemiology of HZ. We examined trends in the incidence of HZ and impact of varicella vaccination on HZ trends using a large medical claims database.

Methods. Medical claims data from the MarketScan® databases were obtained for 1993-2006. We calculated HZ incidence using all persons with a first outpatient service associated with a 053.xx code (HZ ICD-9 code) as the numerator, and total MarketScan enrollment as the denominator; HZ incidence was stratified by age and sex. We used statewide varicella vaccination coverage in children aged 19-35 months to explore the impact of varicella vaccination on HZ incidence.

Results. HZ incidence increased for the entire study period and for all age groups, with greater rates of increase 1993-1996 ($P < .001$). HZ rates were higher for females than males throughout the study period ($P < .001$) and for all age groups ($P < .001$). HZ incidence did not vary by state varicella vaccination coverage.

Conclusions. HZ incidence has been increasing from 1993-2006. We found no evidence to attribute the increase to the varicella vaccine program.

Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus (VZV), the virus that causes varicella. There are an estimated 1 million cases of HZ annually in the United States, with a lifetime risk approaching 1 in 3[1]. About 10%–18% of persons with HZ develop post-herpetic neuralgia (PHN), a disabling pain syndrome that can last months or even years with no consistently effective treatments [1]. About 68% of HZ cases and 85% of PHN cases occur in persons aged ⩾50 years, a population that may be less able to tolerate these conditions and their treatments. Herpes zoster vaccine (HZV), licensed in 2006, can prevent HZ and reduce the risk of PHN among persons who develop HZ despite vaccination [2].

Reasons for reactivation of latent VZV are not fully understood. Recognized risk factors for HZ include increasing age and immunosuppression due to underlying disease or medication use [3]. Some investigators hypothesize that exposure to varicella as well as subclinical reactivation of latent VZV can boost VZV-specific immunity and reduce the risk of HZ [4–6]. In the United States, the varicella vaccine was licensed in 1995. Although uptake increased slowly during the first 5 years of the program, varicella vaccination coverage increased from 68% in 2000 to 89% in 2006 in 19-35 month-olds [7]. Concerns have been raised that the resulting reduction in varicella and exposure to VZV would increase the incidence of HZ [5, 8, 9]. Several studies, including data from other countries with no or limited varicella vaccination programs, suggest that age-specific

Since completion of this study, the affiliation for the following author has changed: Aisha Jumaan, HPV Vaccines Project Director, Program for Appropriate Technology in Health (PATH), Seattle, Washington.

Correspondence: Jessica Leung, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-47, Atlanta, GA 30333 (jleung@cdc.gov).

Clinical Infectious Diseases 2011;52(3):332–340

© The Author 2011. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

1058-4838/2011/523-0001$37.00
DOI: 10.1093/cid/ciq077

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

HZ incidence has been increasing [1, 10–16], and some observers have attributed this trend to the varicella vaccination program. It is necessary to characterize baseline trends of HZ in order to monitor the impact of the HZV program as well as understand changes in the epidemiology of HZ due to varicella vaccination. Herein, we use data from a large medical claims database from 1993, prior to varicella vaccine licensure, to 2006, the year that HZ vaccine was licensed in the United States, to report on trends in HZ. We also evaluate different markers of varicella exposure to better understand its potential impact on the epidemiology of HZ.

METHODS

Data Source

A retrospective cohort study was conducted using data from the MarketScan® databases (Thomson Reuters [Healthcare], Ann Arbor, MI), which include patient-level information from over 100 self-insured employers, state governments, hospitals, health insurance plans, and Medicare, in all states [17]. Data were available from the 1993–2006 MarketScan Commercial Claims and Encounters and its 1996–2006 Medicare Supplemental and Coordination of Benefits databases; they included information on health insurance claims representing current and former employees, retirees, and their beneficiaries. This study was reviewed by the human-subjects coordinator at the CDC and, as an analysis of secondary data without personal identifiers, was determined not to require institutional review board review.

The study population consisted of MarketScan enrollees from January 1993 through December 2006. Data on the enrolled population was abstracted from the 1993–2006 population and the 1998–2006 enrollment tables. Population tables contain aggregate data whereas enrollment tables contain individual-level enrollment data. Outpatient claims data were obtained from the 1993–2006 outpatient services table, which contains data on paid claims for all outpatient physician visits or services, including International Classification of Disease, 9th Revision (ICD-9) diagnostic codes. Because our key study objective was to assess HZ incidence starting before uptake of varicella vaccine was widespread, trends in HZ incidence are based on the population tables for which data were available, starting in 1993.

Ascertainment of Herpes Zoster Cases

A HZ case was defined as an enrollee of any age in the MarketScan database with an outpatient claim bearing a HZ ICD-9 code (053.xx) in the primary or secondary diagnostic position. Enrollees with only PHN-specific ICD-9 codes (053.12, 053.13) were excluded because these cases may not represent incident HZ cases. The initial HZ-related outpatient service or visit between 1 January 1993 and 31 December 2006 was defined as the incident date; subsequent HZ outpatient services or visits were not counted as incident cases as they may represent ongoing HZ episodes.

Statistical Analyses

HZ incidence was calculated by dividing the annual number of incident HZ cases in the MarketScan population tables by the annual MarketScan population, stratified by age and sex using Excel and SAS 9.1 [18]. Overall incidence was age- and sex-standardized to the 2000 US population [19]. A mean test standardized to the 1998–2006 US Census population estimates [19] was performed to examine if the mean age of the HZ cases had changed during the study period.

To control for secular changes in health care access, health-seeking behavior, the composition of the enrolled population, or the databases themselves, we compared trends in HZ incidence with those of 10 preselected conditions that were (1) common, (2) acute in onset, (3) typically medically attended, (4) typically evaluated on an outpatient basis, and (5) had no a priori evidence of changing incidence over time [20]. The selected conditions were impacted cerumen (diagnostic code 380.4), acute pharyngitis (462), kidney/ureter calculus (592.xx), urinary tract infection not otherwise specified (NOS) (599.0), cellulitis of the leg (682.6), ingrowing nail (703.0), lipoma (214.x), wrist/hand sprain (842.xx), blepharitis (373.xx), and unilateral inguinal hernia (550.90); these were ascertained in the outpatient databases in the primary or secondary diagnostic position. The comparison is presented as a simple ratio of number of HZ cases to number of cases for each of the marker conditions with the rate ratio standardized by age and sex to the 2000 US population [19].

The risk of HZ is markedly elevated in immunosuppressed persons [3, 21]. To rule out the possibility that changes in HZ incidence were due to changes in the prevalence of immunosuppression in the study population, we used the enrollment databases to conduct an analysis of HZ incidence in a subset of enrollees. We excluded enrollees with any of 200 ICD-9 codes (Appendix 1) representing conditions that are immunosuppressive or that are at times managed with immunosuppressive drugs or treatments. In preparing this list of conditions, we deliberately erred on the side of overexclusion to ensure that the remaining enrollees were not immunosuppressed. We conducted this analysis in 2 ways: by calculating HZ incidence after excluding all enrollees who had any of the 200 codes at any time during the study interval, and by calculating HZ incidence for each year of the study interval (1998–2006) after excluding enrollees who had any of the 200 codes during that specific year. Results were age-standardized to the 2000 US population [19].

Variation in varicella vaccination coverage among states provided a natural experiment with which to assess whether vaccination influences HZ incidence in the general population.

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

We directly examined HZ incidence in enrollees who resided in states with variable varicella vaccination coverage, based on the coverage assessment of the 1997–2006 National Immunization Survey [7] among children aged 19–35 months. Because there is neither evidence to suggest that specific vaccination-coverage-threshold levels affect HZ rates nor reliable data on the duration of possible protective immunity following external disease exposure, we compared HZ rates in enrollees residing in states that had consistently higher varicella vaccine coverage than the national median during each year from 1997–2006 with HZ rates in enrollees in states with consistently lower coverage. (Enrollees from any state whose status changed during this interval were excluded from this analysis.) For every year during 1998–2006, coverage in all 12 low-coverage states was lower than that in all 13 high-coverage states. We used this strategy because the average number of opportunities for varicella exposure presumably would be lower in high-vaccination-coverage states than in low-coverage states for the entire study interval; the increased incidence of varicella (ie, risk of varicella exposure) in low-coverage states was documented in a MarketScan-based study using this approach [20].

To see whether the incidence of HZ was affected by exposure to varicella, we assessed HZ incidence in enrollees aged 20–50 years with and without at least 1 dependent aged ≤12 years, using young dependents as surrogates for varicella exposure as has been done by others [5, 6, 8, 9]. Analysis was restricted to enrollees in this age group because they were more likely to have household dependents aged ≤12 years.

We performed multivariate analysis as another means to evaluate the association of these variables on HZ incidence. We used a generalized linear model with binomial distribution and log link function, and included the following potential dependent variables in the model: year, age group, sex, region, urban residence (metropolitan statistical area [MSA] status), type of health plan membership, vaccination coverage, and immunosuppressed status (Appendix 1). Because enrollee-level data for these variables in the multivariate analysis were available only from the enrollment databases, this analysis was limited to the years 1998–2006. Variables with a P value $<.05$ were considered significant in the model.

RESULTS

Demographics of Study Population

The enrolled population based on aggregate data from the population table ranged from 3.5 million in 1993 to 10.9 million in 2006 (Appendix 2); 47%–49% were male. The proportion of individuals in each age group remained fairly stable across the study period with the exception of those in the ≥65-year age group. In the years prior to availability of the Medicare data (ie, before 1996), only 1% was in the ≥65-year age group, but in subsequent years, this age group comprised 10%–16% of the MarketScan population. Age distributions and other characteristics of the study population are shown in Appendix 2.

Herpes Zoster Cases

From 1993 through 2006, there were 282,973 incident cases of HZ in our study population. HZ was listed as the primary diagnosis for 96.5% of cases. The mean age of the zoster cases varied little, from 52.5 in 1998 to 53.2 in 2006.

Herpes Zoster Incidence

Throughout the study, HZ incidence varied directly with age (Table 1, Figure 1a) and was higher among females for all age groups ($P < .001$) (Table 1). Incidence increased from 1.7 per 1000 enrollees in 1993 to 4.4 per 1000 in 2006 (Table 1). Increase in overall incidence represented a 98% increase in 13 years, after standardizing by age and sex (Figure 1b). The increases occurred among all age strata and both sexes, increasing more rapidly among females (Table 1). For enrollees aged ≥60 years, increases were still noted when we age-standardized to the 2000 population using 10-year age strata (60–69, 70–79, 80–89, and ≥90 years) for 1998–2006 (data not shown). Increases were detected immediately in 1993–1996 ($P < .001$), but the rates of increase were highest in the earliest part of the study and declined over time ($P < .001$) among adults aged ≥18 years and among children aged 0–17 years. Among children, incidence remained stable after about 2000 (Table 1).

We compared the annual number of HZ codes to codes for 10 preselected conditions, after standardizing by age and sex. The number of HZ cases increased relative to 9 of 10 of these conditions (Figure 2).

HZ incidence increased over time in the immunocompetent population, with higher rates in females (Figure 3a). In this analysis, enrollees were excluded from numerators and denominators for any years in which they had codes for immunosuppressive conditions. Similar trends were noted when we instead excluded enrollees from numerators and denominators for the entire study interval if they had any codes for immunosuppressive conditions during any years during the interval (data not shown).

Age-specific HZ incidence did not differ between adults residing in states with high varicella vaccine coverage and those in low-coverage states ($P = .3173$ for difference in incidence), but it was lower in children living in high-coverage states ($P < .001$). HZ incidence was lower in adults aged 20–50 years with dependents aged ≤12 years compared with adults without dependents ($P < .01$), but became similar over time (Figure 3b). Increasing HZ incidence was also noted using multivariate techniques, after inclusion of age, sex, region, urban residence, and immunosuppressed status (defined in Appendix 1) in the model (data not shown). Since health plan membership and state-level vaccination coverage did not significantly affect HZ

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

Table 1. Herpes Zoster Incidence (Number of cases per 1000 Persons) by Sex and Age Group, MarketScan Enrolled Population, 1993–2006[a]

	Incidence (95% CI), by Sex and Age														
	Males by Age, y							Females by Age, y							Total population
Year	0–17	18–34	35–44	45–54	55–64	≥65	All males	0–17	18–34	35–44	45–54	55–64	≥65	All females	
1993	**0.5** (.4–.5)	**1.0** (.9–1.2)	**1.3** (1.2–1.5)	**2.0** (1.8–2.1)	**3.4** (3.1–3.6)	**5.0** (3.9–6.4)	**1.4** (1.4–1.5)	**0.7**(.6–.8)	**1.2** (1.1–1.3)	**1.5** (1.4–1.7)	**2.7** (2.5–2.9)	**4.8** (4.5–5.1)	**5.0** (3.9–6.4)	**1.9** (1.8–2.0)	**1.7** (1.6–1.7)
1994	**0.7** (.6–.7)	**1.2** (1.1–1.3)	**1.5** (1.4–1.7)	**2.1** (1.9–2.2)	**3.7** (3.5–3.9)	**5.1** (4.1–6.2)	**1.6** (1.6–1.7)	**0.8**(.7–.8)	**1.2**(1.1–1.3)	**1.7** (1.6–1.8)	**2.8** (2.6–2.9)	**5.1** (4.8–5.3)	**4.1** (3.2–5.2)	**2.0** (2.0–2.1)	**1.9** (1.8–1.9)
1995	**0.7** (.6–.7)	**1.0** (.9–1.1)	**1.5** (1.4–1.7)	**2.1** (2.0–2.3)	**3.6** (3.4–3.8)	**5.9** (4.9–7.1)	**1.6** (1.6–1.7)	**0.9**(.8–.9)	**1.3** (1.2–1.4)	**1.7** (1.6–1.8)	**3.1** (2.9–3.2)	**5.0** (4.8–5.3)	**5.7** (4.6–7.1)	**2.2** (2.1–2.2)	**1.9** (1.9–2.0)
1996	**0.7** (.6–.8)	**1.2** (1.1–1.3)	**1.5**(1.4–1.6)	**2.2** (2.1–2.4)	**3.9** (3.6–4.1)	**6.1** (5.8–6.4)	**2.1** (2.1–2.2)	**0.9**(.8–1.0)	**1.4** (1.3–1.5)	**2.0** (1.8–2.1)	**3.4** (3.2–3.5)	**5.1** (4.9–5.4)	**7.0** (6.7–7.3)	**2.9** (2.8–3.0)	**2.5** (2.5–2.6)
1997	**0.8** (.7–.9)	**1.3** (1.2–1.4)	**1.8** (1.7–1.9)	**2.6** (2.5–2.8)	**4.1** (3.9–4.3)	**6.3** (6.0–6.6)	**2.4** (2.3–2.4)	**1.1** (1.0–1.1)	**1.5** (1.4–1.6)	**2.2** (2.1–2.4)	**3.7** (3.5–3.9)	**5.6** (5.4–5.9)	**7.5** (7.3–7.8)	**3.2** (3.1–3.3)	**2.8** (2.8–2.9)
1998	**0.8**(.7–.9)	**1.3** (1.2–1.4)	**1.9** (1.7–2.0)	**2.7** (2.6–2.9)	**4.5** (4.3–4.8)	**6.6** (6.3–6.9)	**2.6** (2.5–2.7)	**1.2** (1.1–1.3)	**1.6** (1.5–1.8)	**2.2** (2.1–2.3)	**3.8** (3.6–4.0)	**6.2** (5.9–6.5)	**8.0** (7.7–8.3)	**3.5** (3.5–3.6)	**3.1** (3.0–3.1)
1999	**0.9** (.9–1.0)	**1.4** (1.3–1.6)	**2.0** (1.8–2.1)	**2.7** (2.5–2.9)	**4.7** (4.5–5.0)	**6.8** (6.4–7.1)	**2.7** (2.6–2.8)	**1.2** (1.1–1.3)	**1.7** (1.6–1.8)	**2.5** (2.3–2.6)	**4.3** (4.1–4.6)	**6.1** (5.8–6.4)	**8.5** (8.2–8.9)	**3.7** (3.6–3.8)	**3.2** (3.2–3.3)
2000	**1.0** (.9–1.1)	**1.5** (1.4–1.6)	**2.1** (1.9–2.2)	**2.8** (2.6–3.0)	**5.0** (4.7–5.3)	**7.4** (7.1–7.8)	**2.8** (2.8–2.9)	**1.3** (1.2–1.4)	**1.9** (1.7–2.0)	**2.6** (2.5–2.8)	**4.3** (4.1–4.6)	**6.4** (6.2–6.7)	**8.7** (8.4–9.1)	**3.8** (3.8–3.9)	**3.4** (3.3–3.4)
2001	**1.0** (.9–1.1)	**1.5** (1.4–1.6)	**2.1** (2.0–2.3)	**2.9** (2.7–3.0)	**5.2** (4.9–5.5)	**8.0** (7.6–8.3)	**3.0** (2.9–3.0)	**1.3** (1.2–1.4)	**1.9** (1.7–2.0)	**2.7** (2.5–2.9)	**4.3** (4.2–4.6)	**7.0** (6.7–7.3)	**9.6** (9.3–9.9)	**4.1** (4.0–4.2)	**3.6** (3.5–3.6)
2002	**1.0** (1.0–1.1)	**1.6** (1.5–1.7)	**2.4** (2.2–2.5)	**3.0** (2.8–3.1)	**4.8** (4.6–5.0)	**6.8** (6.6–7.1)	**3.1** (3.0–3.1)	**1.4** (1.3–1.5)	**2.0** (1.9–2.2)	**2.7** (2.6–2.9)	**4.4** (4.2–4.6)	**6.6** (6.4–6.8)	**8.4** (8.1–8.6)	**4.2** (4.1–4.3)	**3.7** (3.6–3.7)
2003	**1.0** (.9–1.1)	**1.5** (1.5–1.6)	**2.4** (2.2–2.5)	**3.0** (2.9–3.2)	**4.8** (4.6–4.9)	**7.9** (7.6–8.2)	**2.9** (2.8–2.9)	**1.2** (1.1–1.2)	**2.0** (1.9–2.1)	**2.8** (2.7–3.0)	**4.6** (4.5–4.8)	**6.7** (6.5–6.9)	**9.9** (9.6–10.2)	**4.0** (4.0–4.1)	**3.5** (3.4–3.5)
2004	**1.1** (1.0–1.1)	**1.7** (1.6–1.8)	**2.5** (2.3–2.6)	**3.0** (2.8–3.1)	**5.2** (5.0–5.4)	**8.0** (7.7–8.2)	**3.3** (3.3–3.4)	**1.3** (1.3–1.4)	**2.0** (1.9–2.1)	**3.0** (2.9–3.1)	**4.8** (4.7–5.0)	**7.4** (7.2–7.6)	**9.8** (9.6–10.0)	**4.6** (4.5–4.7)	**4.0** (4.0–4.1)
2005	**1.0** (1.0–1.1)	**1.8** (1.7–1.9)	**2.7** (2.6–2.8)	**3.3** (3.2–3.4)	**5.4** (5.3–5.6)	**8.6** (8.4–8.9)	**3.4** (3.4–3.5)	**1.2** (1.2–1.3)	**2.3** (2.2–2.4)	**3.1** (3.0–3.3)	**5.1** (5.0–5.3)	**8.1** (7.9–8.3)	**10.9** (10.7–11.1)	**4.8** (4.8–4.9)	**4.2** (4.1–4.2)
2006	**1.0** (1.0–1.1)	**2.0** (1.9–2.1)	**2.8** (2.7–2.9)	**3.4** (3.3–3.5)	**5.6** (5.5–5.8)	**8.9** (8.7–9.1)	**3.6** (3.6–3.7)	**1.2** (1.2–1.3)	**2.5** (2.4–2.6)	**3.6** (3.5–3.7)	**5.5** (5.4–5.6)	**8.3** (8.1–8.5)	**11.0** (10.8–11.2)	**5.1** (5.0–5.1)	**4.4** (4.3–4.4)

Abbreviation: CI, confidence interval.

[a] Denominator data taken from 1993–2006 MarketScan Population Tables, which contain aggregate enrollment information.

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

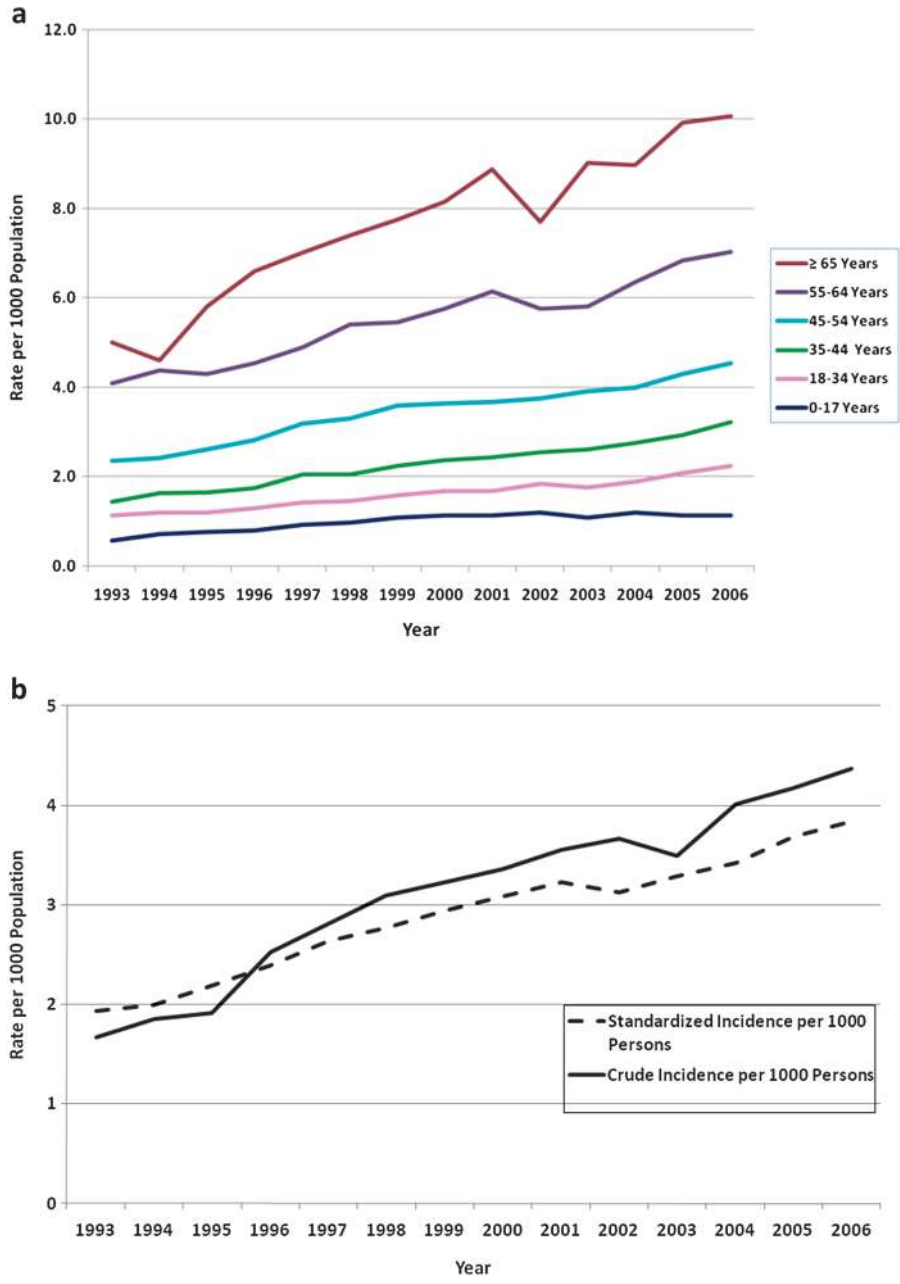

Figure 1a. Annual 1000 persons) in the/1000 persons) by Age Group, MarketScan Enrolled Population, 1993–2006 [a]. [a]Denominator data taken from 1993 –2006 MarketScan Population Tables, which contain aggregate enrollment information.

Figure 1b. Overall Annual 1000 persons) in the/1000 persons), MarketScan Enrolled Population, 1993–2006 [ab]. [a]Denominator data taken from 1993–2006 MarketScan Population Tables, which contain aggregate enrollment information. [b]Data are age- and sex-standardized to the 2000 US Population [19].

incidence in univariate analysis, they were excluded from the final multivariate model.

DISCUSSION

We used a large medical-claims database to show increases in HZ incidence starting as early as 1993–1996. We show that increases in HZ incidence predated vaccine licensure and were most rapid during the early years of the vaccination program, before vaccine uptake reached high levels. We found that HZ rates were similar among those living in high– and low–vaccine coverage states. We did find that adults with dependents aged ⩽12 years had lower HZ incidence at the outset of the varicella vaccination program compared with adults without dependents, and the incidence in both groups became similar as the program progressed. These ecologic analyses suggest that the varicella vaccination program has not influenced HZ incidence in the general population, but it may have affected specific groups at

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

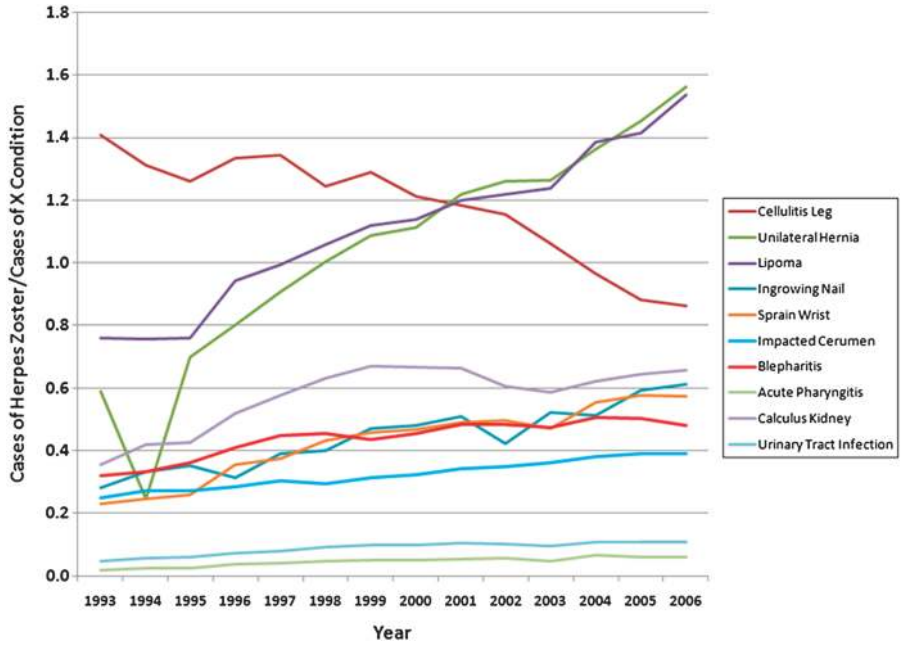

Figure 2. Comparison of Herpes Zoster Incidence to 10 Comparative Conditions, MarketScan Enrolled Population, 1993–2006[a]. [a]Data are age- and sex-standardized to the 2000 US Population [19].

high risk of varicella exposure (eg, adults living with young children). In addition to providing unique data on early effect of varicella vaccination on HZ incidence, these results also provide important baseline information with which to monitor future effects of HZ vaccination.

The age-specific increases in HZ incidence that we document in this study are substantial and robust for all age-strata and both sexes. HZ incidence did, however, stabilize after 1999 among children aged <18 years, the cohort that had been targeted for varicella vaccination. By preventing varicella infection, varicella vaccination has been shown to reduce the risk of HZ in children [22, 23]; our data are consistent with these observations, and suggest that sufficient pediatric varicella vaccination occurred by 2000 to stabilize HZ incidence among children. Several studies conducted in the US and elsewhere [1, 11–16], but not all [24, 25], found that age-specific HZ incidence had been increasing, even before introduction of widespread varicella vaccination [11, 13–16]. Our work strengthens the evidence that age-specific HZ incidence began to increase prior to the initiation of varicella vaccination, and provides a strong indication that these increases were not due to changes in the prevalence of immunosuppression, to secular changes in healthcare access and health seeking behavior, or to other artifacts. Our work also extends earlier findings, showing that the mean age of HZ cases had not changed over time. This is an important observation because the age at which HZ occurs partially determines its clinical severity and the risk of progression to PHN [3, 21, 26].

Our finding that HZ incidence increases with age has been well established; this increase may be related to immunosenescence [3, 21, 26]. We also found that HZ incidence was higher in females. This observation is consistent with many [1, 2, 15, 16, 27–32], but not all [13, 33–35], earlier reports. We believe that the excess HZ incidence we observed in females is a real phenomenon and not due to differential health seeking behavior, since it was observed in all age-cohorts, including children aged 0–17 years. It is unlikely that parents would seek medical care for their children differentially based on gender. There is no known biological or behavioral basis for this excess risk; it does not support the hypothesis that varicella exposure protects against HZ, considering that women are more likely to be the caretakers for their children with varicella.

Although administrative databases provide, at low cost, data on large populations that can be used for surveillance or epidemiologic research, there are limitations to these data. First, claims data can capture information only on HZ cases that seek medical attention. However, results from a population-based survey showed that 95% of 141 adults ⩾60 years of age experiencing HZ sought medical attention during the episode [36]. Also, the accuracy of MarketScan data cannot be validated through record reviews; previous publications have conducted such validation and found that diagnoses are ⩾85% correct [1, 34, 37].

Changes occurred in the makeup of the study population during the study interval. Data regarding Medicare enrollees was not available in MarketScan databases until 1996, so enrollees

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

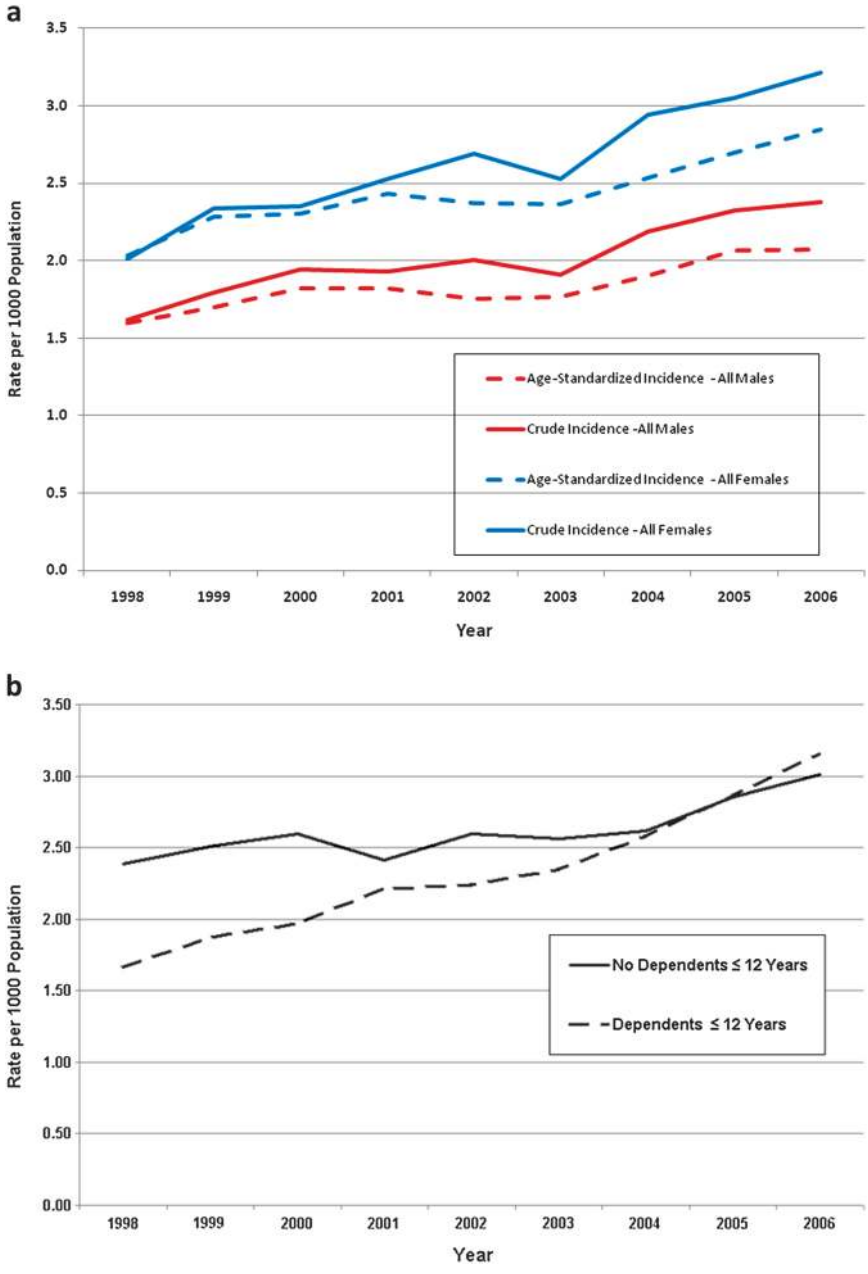

Figure 3a. Herpes Zoster Incidence (cases/1000 persons) in the Immunocompetent Population by Sex, MarketScan Enrolled Population, 1998–2006[abc]. [a]Denominator data taken from 1998–2006 MarketScan enrollment tables, which contain individual-level enrollment information. [b]Data are age-standardized to the 2000 US population [19]. [c]An enrollee's immune status, which was classified for each study year, was determined by whether the enrollee had any of the 200 ICD-9 codes that represented an immunosuppressive condition or a condition that required medications/steroids or therapy that might lead to immunosuppression. See Appendix 1 for a list of relevant ICD-9 codes.

Figure 3b. Herpes Zoster Incidence (cases/1000 persons) Among 20–50-Year-Olds With and Without Dependents Aged ⩽12 Years, MarketScan Enrolled Population, 1998–2006[a].[a]Denominator data taken from 1998–2006 MarketScan enrollment tables, which contain individual-level enrollment information.

aged ⩾65 years were covered by private insurance and may have not been representative of that age cohort. However, whether that cohort was representative, it experienced an increase during those initial years, and the increases noted for all other age cohorts during that interval suggests that the increases were not artifactual. Additionally, managed care health-plan membership and the size of the study population increased. We believe the measures we used, as described, controlled for these changes, but given the gaps in our knowledge of risk factors for HZ, residual unmeasured confounding may have been present in our analyses.

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

There were particular limitations in our analysis of the impact of varicella exposure on HZ incidence. We assumed dependents ⩽12 years of age served as surrogates for varicella exposure to adults in the home. However, identifying young dependents in an administrative claims database is a poorer surrogate than directly asking about presence of children in the home, as was done by others [5, 6, 9]: dependents may not live with enrollees, and children in the home may not be covered by the enrollee's insurance and thus be missed. The rapid convergence of HZ rates among adults with and without young dependents occurring soon after introduction of varicella vaccination also suggests that other, unknown factors may affect HZ rates among adults with dependents aged ⩽12 years.

In conclusion, we found strong evidence of substantial increases in the incidence of HZ across all age groups, which occurred prior to the introduction of the varicella vaccination program. Just why, then, are HZ rates increasing? This question is closely related to the broader question of why one-third of the population experiences HZ during their lifetimes [1], but two-thirds do not. Only a small portion of persons who experience HZ are immunosuppressed, suggesting that unrecognized risk factors are at play. We cannot know why HZ incidence is increasing if we cannot know how key risk factors for HZ are changing. Less well-defined factors that may play roles include comorbid chronic conditions, trauma, psychological stress, race, and family history [3, 8, 38–40]; however, the attributable risk associated with these factors is unlikely to be large or to have changed dramatically over time. Understanding the pathophysiology and epidemiology of HZ is critical for better targeting more effective prevention and treatment strategies.

Acknowledgments

We would like to thank Riduan Joesoef, PhD, for his valuable technical assistance and Dr Stephanie Bialek for her thoughtful review of this manuscript.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

Financial support. None reported.

Potential conflicts of interest. All authors: no conflicts.

References

1. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc **2007**; 82:1341–9.
2. Oxman MN, Levin ML, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **2005**; 352:2271–84.
3. Harpaz R, Ortega-Sanchez IR, Seward JF. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control Prevention (CDC). Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2008**; 57:1–30.
4. Hope-Simpson RE. The nature of herpes zoster: A long-term study and a new hypothesis. Proc R Soc Med **1965**; 58:9–20.
5. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: A case-control study. Lancet **2002**; 360:678–82.
6. Donahue JG, Kieke BA, Gargiullo PM, et al. Herpes zoster and exposure to the varicella zoster virus in an era of varicella vaccination. Am J Public Health **2010**; 100:1116–1122.
7. Centers for Disease Control and Prevention. National immunization survey (NIS). Available at: http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm#nis. Accessed 8 February 2010.
8. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis **2004**; 4:26–33.
9. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: Implications for mass vaccination against chickenpox. Vaccine **2002**; 20:2500–7.
10. 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:S224–7.
11. Pérez-Farinós N, Ordobás M, García-Fernández C, et al. Varicella and herpes zoster in Madrid, based on the Sentinel General Practitioner Network: 1997–2004. BMC Infect Dis **2007**; 7:59.
12. Yih WK, Brooks DR, Lett SM, 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.
13. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) **1982**; 61:310–6.
14. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect **2001**; 127:305–14.
15. Russell ML, Schopflocher DP, Svenson L, Virani SN. Secular trends in the epidemiology of shingles in Alberta. Epidemiol Infect **2007**; 135:908–13.
16. Toyama N, Shiraki K; Society of the Miyazaki Prefecture Dermatologists. Epidemiology of herpes zoster and its relationship to varicella in Japan: A 10-year survey of 48,388 herpes zoster cases in Miyazaki prefecture. J Med Virol **2009**; 81:2053–8.
17. Thompson Healthcare Inc. MarketScan databases user guide and database dictionary, commercial and medicare supplemental databases, 2006 edition. Englewood, CO: Thompson Healthcare Inc, 2007.
18. SAS Institute Inc. SAS OnlineDoc. Version 9.1. Cary, NC: SAS Institute Inc, 2004.
19. US Census Bureau. Population profile of the United States. Available at: http://www.census.gov Accessed 11 December 2009.
20. Zhou F, Harpaz R, Jumaan AO, Winston CA, Shefer A. Impact of varicella vaccination on health care utilization. JAMA **2005**; 294:797–802.
21. Gnann JW Jr. Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med **2002**; 347:340–6.
22. Tseng HF, Smith N, Marcy SM, Sy LS, Jacobsen SJ. Incidence of herpes zoster among children vaccinated with varicella vaccine in a prepaid health care plan in the United States, 2002–2008. Pediatr Infect Dis J **2009**; 28:1069–72.
23. Civen R, Chaves SS, Jumaan A, et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementation of varicella vaccination. Pediatr Infect Dis J **2009**; 28:954–9.
24. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. J Infect Dis **2005**; 191:2002–7.

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022

25. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997–2002. Epidemiol Infect **2005**; 133:245–53.
26. Schmader K. Herpes zoster and postherpetic neuralgia in older adults. Clin Geriatr Med **2007**; 23:615–32.
27. Chapman RS, Cross KW, Fleming DM. The incidence of shingles and its implications for vaccination policy. Vaccine **2003**; 21:2541–7.
28. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med **2005**; 20:748–53.
29. Fleming DM, Cross KW, Cobb WA, Chapman RS. Gender difference in the incidence of shingles. Epidemiol Infect **2004**; 132:1–5.
30. Opstelten W, van Essen GA, Schellevis F, Verheij TJM, Moons KG. Gender as an independent risk factor for herpes zoster: A population-based prospective study. Ann Epidemiol **2006**; 16:692–5.
31. Chidiac C, Bruxelle J, Daures JP, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. Clin Infect Dis **2001**; 33:62–9.
32. Gauthier A, Breuer J, Carrington D, Martin M, Rémy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect **2009**; 137:38–47.
33. 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**; 24:1308–14.
34. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med **1995**; 155(15);1605–9.
35. Di Legami V, Gianino MM, Atti MC, et al; and Zoster Study Group. Epidemiology and costs of herpes zoster: Background data to estimate the impact of vaccination. Vaccine **2007**; 25:7598–604.
36. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: Uptake of the first new vaccine to target seniors. Vaccine **2009**; 27:882–7.
37. Komplas M, Bialek S, Harpaz R. Automated surveillance for herpes zoster and postherpetic neuralgia using structured electronic medical record data. In: Program and postherpetic abstracts of the 8th Annual International Society for Disease Surveillance Conference (Miami). Boston, MA: International Society for Disease Surveillance, 2009. Available at: http://www.syndromic.org/annual-conference/2009. Accessed 20 August 2010.
38. Thomas SL, Wheeler JG, Hall AJ. Case-control study of the effect of mechanical trauma on the risk of herpes zoster. BMJ **2004**; 328:439.
39. Nagasako EM, Johnson RW, Griffin DR, Elpern DJ, Dworkin RH. Geographic and racial aspects of herpes zoster. J Med Virol **2003**; 70:S20–3.
40. Hicks LD, Cook-Norris RH, Mendoza N, Madkan V, Arora A, Tyring SK. Family history as a risk factor for herpes zoster: A case-control study. Arch Dermatol **2008**; 144:603–8.

Downloaded from https://academic.oup.com/cid/article/52/3/332/305169 by guest on 21 August 2022