BRIEF REPORT



The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Older Adults

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(See the Brief Report by Harpaz and Leung on pages 345–7.)

Historic herpes zoster incidence trends in US adults have been hard to interpret. Using administrative databases, we extended previous descriptions of these trends through 2016. We observed an age-specific transition, with ongoing increases among younger adults but deceleration in older adults. The patterns are not readily explained.

Keywords. zoster; shingles; vaccine.

The age-specific incidence of herpes zoster (HZ) in the United States has increased dramatically over the past half-century, although the reasons remain obscure [1-4]. There is no clear evidence to support the most obvious explanations, including increases in ascertainment, the use of immunosuppressive agents, or a prevalence of chronic comorbid conditions [1-5]. In addition, there is substantial evidence to challenge the hypothesis that the increasing trends result from declines in exposure to varicella following the introduction of a varicella vaccine in 1996 (ie, with attendant reductions in exogenous immunological boosting) [5-7]. Regardless, as long as the causes for the increases remain unresolved, these trends need to be monitored to better assess the population burden of HZ and its complications, and to interpret the true impact of HZ vaccines [8].

The Food and Drug Administration licensed Zostavax (ie, zoster vaccine live; ZVL) for the prevention of HZ among adults aged ≥ 60 years in 2006, and extended the indication to adults aged ≥ 50 years in 2011. The Advisory Committee for Immunization Practices has recommended ZVL to adults aged ≥ 60 years since 2008. ZVL uptake has increased by ~3–3.5%

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annually among adults aged ≥ 60 years, reaching 33% by the end of 2016 [9]; uptake then was 5% among adults aged 50–59 years (unpublished data, Centers for Disease Control and Prevention).

We have previously shown that the age-specific HZ incidence increased from 1993 through 2006 [3]. In the current report, we extend our earlier analysis by 10 years to better define background trends during the era of varicella and HZ vaccines.

METHODS

Data Sources

We conducted a retrospective cohort study of HZ incidence using data from IBM MarketScan[®] Research Databases, which include data from public and private employers, health insurance plans, and Medicare; we excluded data from health insurance plans, for which the enrollment numbers have been more unstable over time. We analyzed data from 2 MarketScan sources. First, we used data from population tables from the years 1993–2015. These tables contain aggregate data that provide the longest look back possible, but the age-stratification is fixed and the tables stopped being maintained after 2015. Second, we used data from enrollment tables from the years 1998–2016. These tables contain individual-level data, which allow more analytic flexibility, including age-strata that better matched ages targeted by the HZ vaccine program. For both data sources, we used the same methods that we used in our previous publication [3].

Case Finding

The primary focus of this analysis was on adults aged \geq 35 years; we focused on children in a separate analysis [10]. HZ cases were defined using outpatient and emergency department claims, with International Classification of Diseases, Ninth and Tenth Revisions (ICD-9/10) diagnostic codes for HZ (053.xx/B02. xx) in the primary or secondary diagnostic position, excluding prevalent postherpetic complications (053.12-053.13/B02.2x). HZ diagnostic codes map almost 1-to-1 from ICD-9 to ICD-10. We only used initial HZ-related codes in an individual, representing an incident HZ event.

Statistical Analyses

Age-specific HZ incidence was calculated by dividing the annual, age-specific number of incident HZ cases by the annual, age-specific MarketScan population. We performed a multivariate analysis, using a generalized linear model with a binomial distribution and log link function, to evaluate the association of age group and sex on HZ incidences. Any 2-sided P values <.05 were considered statistically significant. We used the Pearson chi-square test to evaluate differences in the distribution of HZ cases by age groups over the study period.

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RESULTS

Herpes Zoster Cases

There were a total of 27 262 603 persons aged \geq 35 years in our prospective study; enrollment in the databases increased over time (median enrollment: 2092 106 during 1998–2002 and 9833 869 during 2012–2016). The median follow-up for this rolling cohort was 49 months (interquartile range, 24–85 months).

In the population tables (ie, 1993–2015) and enrollment tables (ie, 1998–2016) there were 934 340 and 804 029 incident HZ cases, respectively, among persons aged \geq 35 years; 92% of cases in both tables coded in the primary diagnostic position. In an unadjusted analysis, 62% of the total cases occurred among women, and the age distributions remained stable: between 1993–2003 and 2004–2016, the mean ages were 59.4 and 59.3 years, respectively.

Herpes Zoster Incidence

In adjusted analysis, the well-recognized association between HZ incidence and age that we reported for 1993–2006 persisted through 2016 (Figure 1A), as did the higher HZ incidence among females in the full cohort (relative incidence rate 1.38, 95% confidence interval 1.38–1.39; P < .0001). The HZ incidence, which had increased from 2.5/1000 in 1993 to 6.1/1000 in 2006 among adults aged \geq 35 years, continued to increase, to 7.2/1000 in 2016, but the patterns varied by age strata (Figure 1). We focus on the findings among children in a separate publication [10].

DISCUSSION

We extended our previous analysis of HZ incidence by 10 years, through 2016, to better interpret the impacts of the varicella and HZ vaccine programs [3]. In general, the age-specific increases that we reported for the years 1993–2006 persisted, but there were striking differences by age group: HZ incidence has continued to increase in a generally steady manner among the younger adult age strata (ie, ages 35 through 50–55 years), without any clear accelerations or decelerations during the study interval. However, among the older age strata (ie, ages \geq 50–55 years), the comparable rise in HZ incidences that occurred through 2006 appears since to have decelerated.

Regarding the trends among younger adults, increases in HZ incidences have been reported among all age groups, going back decades [1–4]. Suggested explanations have included changes in health care–seeking behavior, leading to better case-finding, and increases in the age-specific HZ risk, due to a growing prevalence of immunocompromising or other chronic conditions. Neither of these explanations has stood up to careful examination [1–5].

Our current findings regarding older adults seem to further confuse the complex epidemiology of HZ: we are unable to fully explain the rapidly changing trajectory in HZ incidences in these older strata, or the degree of divergence in trajectories by age group, just as we have been unable to explain the previous, increasing trends.

Availability of ZVL surely must have impacted HZ incidence, as it has in England [11], but it seems unlikely that the abruptness of the changes in trajectory among older adults could be fully attributed to ZVL. First, ZVL uptake among adults aged ≥60 years began slowly, increasing from 2-14% from 2007 to 2010 and reaching 33% by 2016 [9]; among adults aged 50-59 years, uptake during 2008-2016 ranged from 3-6% (unpublished data, Centers for Disease Control and Prevention). Second, initial ZVL efficacy in adults is imperfect, at 70%, 64%, 41%, and just 18% among adults aged 50-59, 60-69, 70-79, and ≥80 years, respectively [12]. Finally, ZVL uptake data derive from self-reported responses to the question "have you ever received ZVL," so they do not allow for direct determinations of age at vaccination or time since vaccination: thus, the 33% of respondents reporting ZVL uptake in 2016 could have been vaccinated up to 10 years earlier, by which time a substantial portion of the vaccine's protection had waned from the initial values [8]. The slopes of the age-specific curves and the timing of any apparent inflection points do not seem to bear obvious relationships to the timing, uptake, or efficacy of the vaccine.

Evidence that HZ incidence in unvaccinated or minimally vaccinated adults plateaued during the latter part of last decade has also been reported from other study settings, although the primary data have not been explicitly presented in peer-reviewed publications [6]. Short of such publications, the only way to definitively resolve whether the deceleration in HZ incidence among older adults can be attributed to the ZVL program would be to directly explore this possibility in formal simulations, using plausible parameters. (A second vaccine for the prevention of HZ was licensed in 2017, and would not influence our findings).

Others have proposed that declines in exposure to varicella following the introduction of varicella vaccination would have reduced varicella-zoster virus-specific immunological boosting, and thereby increased the HZ incidence among adults. Modelers have predicted that the increased incidence would be substantial and immediate [6, 7]. Our results challenge these predictions: varicella circulation declined rapidly following the introduction of varicella vaccination in 1996, with reductions in reported cases of >95% by 2014 [6]. Not only have we observed no evidence of accelerating HZ incidence over that time interval, but we now report deceleration among older adults. We know of no parsimonious or cohesive explanations of how the varicella vaccination program could cause these patterns among adults. It is noteworthy, however, that our data show declines in HZ incidences among children (Figure 1A); we discuss these findings elsewhere and consider their explanations at length [10].

Our analysis has limitations. MarketScan databases capture a very large population, but the data are based on a large convenience sample and the population is disproportionately drawn from employer-based insurance and is, thus, not fully representative. Administrative claims data, and indeed all health-sector-derived data, only capture information on medically attended HZ cases.



Figure 1. Herpes zoster incidence as a function of calendar year, from MarketScan databases: (A) population tables, 1993–2015, and (B) enrollment tables, 1998–2016. For all cells, the denominators ranged in size from 469 000 to 4.6 million, with the exception of 3 values (25 000–35 000 for cells representing persons aged \geq 65 years, during 1993–1995). Abbreviation: HZ, herpes zoster.

While over 90% of adults experiencing HZ seek healthcare, the proportions may vary by age or over calendar time [13]. We did not control our analysis for factors such as immunocompromise,

health-care practices, or chronic conditions; we had conducted such controls during our prior analysis and they did not substantially change our analysis [3]. Finally, as noted above, we did not have access to detailed data regarding ZVL uptake that would have permitted us to formally evaluate our contention that HZ incidence has been decelerating more than expected.

There are an estimated million episodes of HZ annually in the United States [14], often causing significant pain, suffering, and disability. This substantial burden provides rationale for continuing to monitor patterns of HZ incidences. Fortunately, vaccines are now available to reduce that HZ burden [14, 15]. Nonetheless, given the seeming unpredictability of HZ incidences over time, researchers and public health practitioners need to be cautious in interpreting or attributing those patterns.

Notes

Author contributions. R. H. and J. W. L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. H. conceived, designed, and supervised the study. J. W. L. acquired the data. R. H. and J. W. L. analyzed and interpreted the data, drafted the manuscript, and performed the statistical analyses.

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