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

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(See the Brief Report by Harpaz and Leung on pages 341–4.)

Varicella vaccination can have complex direct and indirect influences on the epidemiology of herpes zoster among children. We evaluated pediatric herpes zoster trends using administrative databases. The incidence has declined in a step-wise pattern since the varicella vaccination program’s introduction, suggesting that rates may eventually decline in the entire population.

Keywords. zoster; shingles; varicella; chicken pox.

Prior to the licensure of the varicella vaccine in the United States, almost the entire population experienced infection with the varicella zoster virus (VZV), causing varicella [1, 2]. The hospitalizations, deaths, and economic impacts resulting from these illnesses prompted the development and licensure of the varicella vaccine, with a 1-dose recommendation for children issued in 1996 [3]. While the varicella vaccine is effective, typically-mild breakthrough varicella infections continued to occur, leading to an added second-dose recommendation in 2006 [3]. The 1- and 2-dose varicella vaccine coverage increased steadily over time [4], leading to concurrent declines in varicella incidences within years after the vaccination was first recommended, with rates reduced by 97% by 2014 [5].

VZV infection is an absolute prerequisite for herpes zoster (HZ): a primary infection leads to varicella and, as it resolves, VZV establishes a latent infection in the dorsal root ganglia, from where it may reactivate to cause HZ years to decades later (although latency may be shorter and the risk of pediatric HZ is increased when VZV infection occurs prenatally or during infancy) [2, 6]. The live-attenuated VZV contained in the varicella vaccine (v-VZV) can also cause HZ; the risks appear to be less than those for wild-type VZV (wt-VZV), but they remain incompletely defined [7, 8].

While the epidemiology of HZ in adults has been changing for unrecognized reasons [9], the varicella vaccination program may have had distinct, complex influences on the epidemiology of HZ among children who either would have had the opportunity to be vaccinated or were young enough when the vaccine program was established to be impacted indirectly by the resulting declines in risks of infection (ie, “herd protection”). Herein, we report the results of an analysis of HZ trends in children from the years 1998 through 2016.

METHODS

Our analysis was based on IBM MarketScan® Research Databases for the years 1998–2016. MarketScan databases include data from public and private employers, health insurance plans, and Medicare, and for individuals residing in all states. We considered incident HZ cases among enrollees, 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). Of note, the diagnostic codes for HZ map almost 1-to-1 from ICD-9 to ICD-10. For a given person, we only included the first HZ episode during the study period. HZ trends were analyzed using data on children aged <18 years; a secondary analysis of age-specific HZ rates included persons aged <35 years. Age-specific HZ incidence was calculated by dividing the annual, age-specific number of incident HZ cases in the MarketScan outpatient claims by the annual, age-specific MarketScan population.

RESULTS

There were a total of 13 084 793 children aged <18 years enrolled during our 1998–2016 study interval; their numbers grew annually from 679 437 (median, 1998–2002) to 3 840 458 (median, 2012–2016). This rolling cohort represented 51 million person-years of follow-up; the median follow-up was 37 months (interquartile range 12–61 months), and was fairly stable over time. There were 35 405 incident HZ cases among these children; 95% were coded in the primary diagnostic position. HZ incidence changed in each age stratum, showing increases followed by decreases in a step-like manner (Figure 1A). The peak incidence occurred in progressively-earlier calendar years among progressively-younger strata, with all occurring among cohorts born approximately between 1990 and 1996; the incidences declined from peak values by about 70–80% in the

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different age cohorts, with absolute values as low as 0.22 per 1000 among children in each of the 2 youngest age strata. For each age stratum, differences in HZ incidences by sex appeared to sharply converge as the incidences declined (Figure 1B). The HZ incidences increased by age during childhood and early adulthood in individuals born prior to 1996, but age-specific HZ incidences flattened out for later birth cohorts (Figure 1C).

**DISCUSSION**

We made 3 important observations in our analysis. We found that HZ incidences have declined dramatically among children since 1998, as the varicella vaccination program was being introduced and was maturing [4]; that an excess HZ incidence, which was seen in girls as compared to boys, disappeared among age cohorts born after the varicella vaccine licensure; and that age, an established risk factor for HZ among older adults, was associated with HZ incidences even among children and young adults. We discuss each of these observations sequentially.

The declining HZ incidences over time among children in our analysis followed a striking step-wise pattern that can be explained by 3 contributing phenomena: secular trends in HZ incidences, the changing distribution of latent VZV strains over time, and VZV strain-specific differences in HZ risks.

Regarding secular trends, age-specific increases in HZ incidences have been noted across all age groups during past decades in the absence of varicella vaccination, in the United States and elsewhere [9]. Regarding the changing distribution of VZV strains (ie, wt-VZV versus v-VZV) among persons born during or before the early 1980s, when varicella was endemic, well over 90% experienced the illness and were, thus, permanently infected with wt-VZV [1]. In contrast, among persons born since about 2010, after wt-VZV circulation plummeted, over 90% received at least 1 dose of the varicella vaccine and most were exclusively infected with v-VZV [4, 5]. During the intervening years, in successive birth cohorts, an almost-complete replacement of wt-VZV infection by v-VZV infection occurred, accompanied during this transition by varying mixtures of wt-/v-VZV infections (ie, either from vaccination followed by infection, due to vaccine failure, or from infection followed by vaccination). This was nicely documented in a study of vaccinated children aged <18 years who developed HZ during 2005–2008: whereas about half of the total episodes yielded wt-VZV, that portion declined considerably by calendar year at birth as the varicella circulation declined [8]. Throughout, a fourth, less common, status consisted of VZV-negative persons who escaped both varicella and vaccination altogether. Regarding the strain-specific risks of HZ, the risk from v-VZV appears to be a fraction of that of wt-VZV, with the risk of mixed wt-/v-VZV infections presumably intermediate [7, 8].

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**Figure 1.** Herpes zoster incidence in children aged <18 years by (A) age group and (B) age group and sex, as a function of calendar year, and (C) in individuals aged <35 years, as a function of age (MarketScan databases). Varicella vaccination was introduced in 1996, and 1-dose coverage in children 19–35 months of age reached ≥80% in 2002 and ≥90% in 2006; following second-dose recommendations in 2007, 2-dose coverage in children 7 years of age reached ≥80% by 2012. [4] For all cells, the denominators ranged in size, from 51,269–796,456 in A, 24,890–1,036,759 in B, and 3826–2,726,254 in C (excluding 3826 as an outlier, the range would be 36,554–2,726,254). Abbreviation: HZ, herpes zoster.
We postulate that HZ incidences in wt-VZV infected children increased prior to the introduction of varicella vaccination, just as they increased among adults [9]. With vaccine introduction, the high-risk wt-VZV strain was replaced, birth cohort by birth cohort, by the low-risk v-VZV strain, so that HZ rates plateaued and began a steady decline. Declining wt-VZV circulation lowered the likelihood of prenatal and infant infection, further contributing somewhat to the reduced risk of pediatric HZ [6]. Declines in HZ incidences have been documented in analyses involving smaller numbers of children following the introduction of varicella vaccination [7,8,10,11]; the step-wise pattern that we report provides graphic support for this explanation. Our results suggest that, over decades, this declining HZ incidence will extend to progressively older adults, ultimately extending to the entire population. Our results also suggest that over time, it may be possible to estimate the risk of HZ among persons with exclusive v-VZV latency: currently, that incidence seems to be converging at about 0.2 per 1000, but it may be too soon to settle on a value. The trajectory in the figures had not yet plateaued, so rates may decline further; on the other hand, the rates may reflect a few percent of VZV-negative children, who would be at 0 risk of HZ, resulting in an underestimate of the v-VZV–associated HZ risk.

We also found that different HZ incidences in girls versus boys converged after varicella vaccine licensure. A higher age-specific HZ incidence among females versus males has been repeatedly documented and remains unexplained [2,12], but finding this discrepancy among premenarchal children makes both hormonal differences and variations in health-seeking behavior less plausible. The convergence occurring among mostly v-VZV–infected children is surprising and may relate to subtle biological differences in v-VZV reactivation by gender, but see our discussion of limitations below for a second plausible explanation.

Finally, we found that HZ risk increases with age, even among children and young adults. This increase cannot be explained by the simple acquisition of VZV infection by age (ie, without which HZ is impossible), since the slope of the HZ increase is considerably steeper than that for VZV seropositivity by age [1]. Our results raise the provocative possibility that age-related increases in HZ risk among older adults, too, may be due to more than immunosenescence alone. Interestingly, for children born after 2002, during the vaccine era, age does not appear to be associated with HZ incidence, although more years of data will be needed to verify these incomplete data.

The limitations relating to the use of administrative data are well recognized; we describe many elsewhere [12]. In the context of children, the ascertainment of HZ can be a particularly important confounder. Not only is pediatric HZ uncommon, but its rash and pain manifestations are mild in the youngest children, becoming more adult-like in painfulness throughout childhood [6,8]. Manifestations in v-VZV–infected children may be milder still [6]. Milder cases may not come to medical attention, or may be misdiagnosed. Variation in HZ ascertainment by age and VZV strain may partially explain either the declines in HZ among vaccinated cohorts or the increases in HZ with age. It is even plausible that parental health-seeking for children may vary by gender, particularly since girls may experience more HZ pain than boys [8], and that such behavior could lead to a convergence of HZ incidences among vaccinated cohorts if HZ caused by v-VZV is less painful [7].

HZ can be disabling among older adults, but it continues to surprise and confound. Our results, that the HZ incidence is declining following the introduction of varicella vaccination, provide tentative reassurance that over time, rates of HZ will decline throughout the entire population.

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 statistical analyses.

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