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Seasonality of Herpes Zoster and Herpes Zoster Ophthalmicus

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Abstract

Background: Herpes zoster (HZ) and herpes zoster ophthalmicus (HZO) are common and debilitating diseases. There is no consensus in the literature whether HZ and HZO exhibit seasonal patterns.

Objectives: To determine whether HZ and HZO are seasonal.

Study design: All patients in the OptumLabs® Data Warehouse (OLDW), a longitudinal, insurance claims database with de-identified lives between January 1, 2006 and December 31, 2017 with 365 days or more of continuous enrollment were considered in the study. The database was queried for patients reporting a new ICD-9/ICD-10 code for HZ or HZO and monthly counts of each administrative code were modeled using Morelet wavelets and analyzed for annual periodicity using Fisher's g test.

Results: There were a total of 513,911 new cases of HZ during this time period; 40,166 cases (7.8%) were reported as HZO. Administrative coding for new cases of HZ exhibited annual periodicity ($P<.001$) with a peak in the summer. No periodicity was evident for HZO.

Conclusions: These results contribute to a growing body of evidence suggesting that HZ may be seasonal and help characterize the epidemiology of this common, painful disease.

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Competing Interests

None declared.

Ethical Approval

This study was granted an exemption from the UCSF institutional review board because it used a pre-existing, de-identified dataset. All authors (Elyse Berlinberg, Eric Kim, Michael Deiner, Casey Patterson, Travis Porco and Nisha Acharya) made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Keywords

herpes zoster; shingles; herpes zoster ophthalmicus; seasonality; epidemiology; wavelets

Background

One in three Americans will experience herpes zoster (HZ or shingles) in their lifetime.[1] HZ is caused by a reactivation of the varicella zoster virus (VZV) in the sensory ganglia. Reactivation of VZV in the ophthalmic division of cranial nerve V is called herpes zoster ophthalmicus (HZO) and accounts for 10–20% of all HZ cases.[2] There has been considerable debate about whether HZ exhibits a seasonal pattern, with some reports claiming an increase of HZ cases in the summer and others claiming no significant evidence of an annual trend.[3] We report a time-series analysis on data from a large insurance database to identify any seasonal trends in cases of HZ and HZO in the United States.

Objective

We aim to determine whether there are seasonal trends in the incidence of HZ and HZO using time-series analysis.

Study design

We conducted a time-series analysis of the first occurrence of the administrative code for herpes zoster (ICD-9: 053.X and ICD-10: B02X) and herpes zoster ophthalmicus (ICD-9: 053.2 and ICD-10: B023.X) from the OptumLabs Data Warehouse, OLDW, Optum Labs Inc, Cambridge, MA, USA. Wavelet analysis is a form of statistical analysis that is used to identify trends in quantitative data over a period of time. This method compares the changes in a value over time to identify statistically significant extreme values in the data. In particular, wavelet analysis has been increasingly utilized in research on the epidemiology of infectious disease to identify seasonal peaks. OLDW is an insurance claims database containing de-identified data from >200 million patients in the United States enrolled in commercial insurance, Medicare Advantage, or Medicare Part D plans from 1993 to present. The sample was limited to patients who had ≥ 365 days of continuous enrollment to prevent chronic or historical cases of HZ and HZO from being included in the dataset. Time-series analysis was conducted by creating a periodogram of average monthly diagnosis counts between January 1, 2006 and December 31, 2017. Data was normalized using a denominator of all patient encounters for persons enrolled in the OLDW with ≥ 365 days of continuous enrollment. To test significance of periodicity, we first fit a generalized additive model with a spline term representing an unspecified secular trend. We then added two trigonometric terms A cos φ and B sin φ to account for seasonality and used time series bootstrap to test the null hypothesis of no seasonality. The peak month was calculated from the estimated values of the trigonometric coefficients A and B. Secondary analyses of the time series data were performed by separating the dataset into four groups by geographic region as utilized by the US Census Bureau (https://www.census.gov/geo/): Midwest, Northeast, South, and West. In addition, we computed a normalized relative incidence w_i for each month. This normalized relative incidence facilitates comparison of the seasonal pattern independent

of the overall scale; a normalized relative incidence greater (less) than one corresponds to a value greater (less) than the mean monthly incidence. A *P*-value of less than .05 was considered statistically significant. All statistical tests were conducted in R version 3.5 for MacIntosh (The R Foundation for Statistical Computing, Vienna, Austria). This study was granted an exemption from institutional review board approval because it used a pre-existing, de-identified dataset.

Results

513,911 patients in the OLDW had a new administrative code for HZ between May 26, 2006 and December 31, 2017. Of these patients, a code for HZO was identified in 40,166 unique patients (7.8%). Time series analysis of dates of encounters with a code for HZ indicated a statistically significant annual cycle ($P<.001$). For both raw (unnormalized) counts, as well as coding normalized to total monthly patient encounters, the peak occurred in August (Figure 1a). This trend persisted in a secondary analysis by geographic region dividing the dataset into patients from the Midwest ($P<.001$), Northeast ($P<.001$), South($P<.001$), and West ($P<.001$).

Time series data for HZO revealed no statistical evidence of an annual cycle ($P=.34$). Similar results were obtained by region: Midwest ($P=.64$), Northeast ($P=.71$), South ($P=.24$), and West ($P=.51$) United States (Figure 1b).

Discussion

The findings from this study suggest that HZ is seasonal, with HZ cases peaking in the summer, but HZO does not appear to have a statistically significant seasonal trend. Previous studies have varying conclusions on whether HZ is seasonal. A 2004 review of risk factors for HZ reported that the majority of past seasonality studies did not suggest a seasonal trend for HZ.[3] However, the majority of these earlier studies were single-practice reports limited by small study populations and low generalizability. More recent studies utilizing larger, more diverse datasets have produced varied results. Of seasonality studies published within the last 10 years analyzing a population greater than 1 million individuals, three studies from Japan, Australia, and Taiwan have reported a seasonality with greater incidence of HZ in the summer while two studies from Perth, Australia and South Korea have reported no seasonal variation.[4–8] Many of these studies infer that seasonal trends in HZ may be related to UV exposure, with greater UV intensity in the summer influencing re-activation of the varicella virus. UV exposure has already been implicated as a risk factor for reactivation of another alpha human herpes virus infection, herpes simplex (HSV).[9,10] While few studies have assessed this claim in HZ, the aforementioned study from Perth, Australia found a significant correlation between HZ cases and UV index.[7] An important next step is to compare these data on HZ trends to the United States UV index data.

To date, the current study is the largest dataset analyzed for the seasonality of HZ and the first to be analyzed for the seasonality of HZO. The current analysis adds to a growing body of evidence suggesting that HZ may exhibit a seasonal pattern. HZ and HZO cause significant morbidity that may lead to painful post-herpetic neuralgia and blindness, so a

better understanding of potential risk factors that may be modifiable in preventing these conditions is important.[1]

There are some limitations to consider. OptumLabs conducts monthly updates to improve coding accuracy, but it is possible that HZ and HZO could be miscoded or underreported in the OLDW. The proportion of HZ codes that were specific for HZO in our dataset, 7.8%, is slightly lower than reported in the literature (10–20%).[2] Providers may list the administrative code for the more general “HZ”, rather than the more specific “HZO”, resulting in underrepresentation of HZO cases. Furthermore, some “new” codes for HZ and HZO could represent the first time a patient presents with a recurrent or chronic zoster infection after switching insurance to a different plan rather than a new diagnosis, but we would expect this to be rare given the 1-year continuous enrollment requirement. Finally, this analysis is only able to establish an association, not causation. The biological processes that could explain a possible seasonal reactivation of latent varicella zoster virus are still unknown.

In conclusion, the incidence of HZ as reported by administrative codes suggests that this disease exhibits an annual trend with a peak in the summer. Further studies are needed to understand the mechanisms underlying this seasonal trend and whether there are modifiable risk factors.

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Highlights

- There is no consensus in the literature whether herpes zoster and herpes zoster ophthalmicus exhibit seasonal patterns.
- This study used a large, longitudinal, insurance claims database between 2006 and 2017 to assess whether herpes zoster and herpes zoster ophthalmicus are seasonal.
- There were a total of 513,911 new cases of herpes zoster during this time period, and 7.8% were reported as herpes zoster ophthalmicus.
- Herpes zoster exhibited annual periodicity ($P<.001$) with a peak in the summer.
- No periodicity was evident for herpes zoster ophthalmicus.
- These results suggest that herpes zoster may be seasonal and help characterize the epidemiology of this common, painful disease.

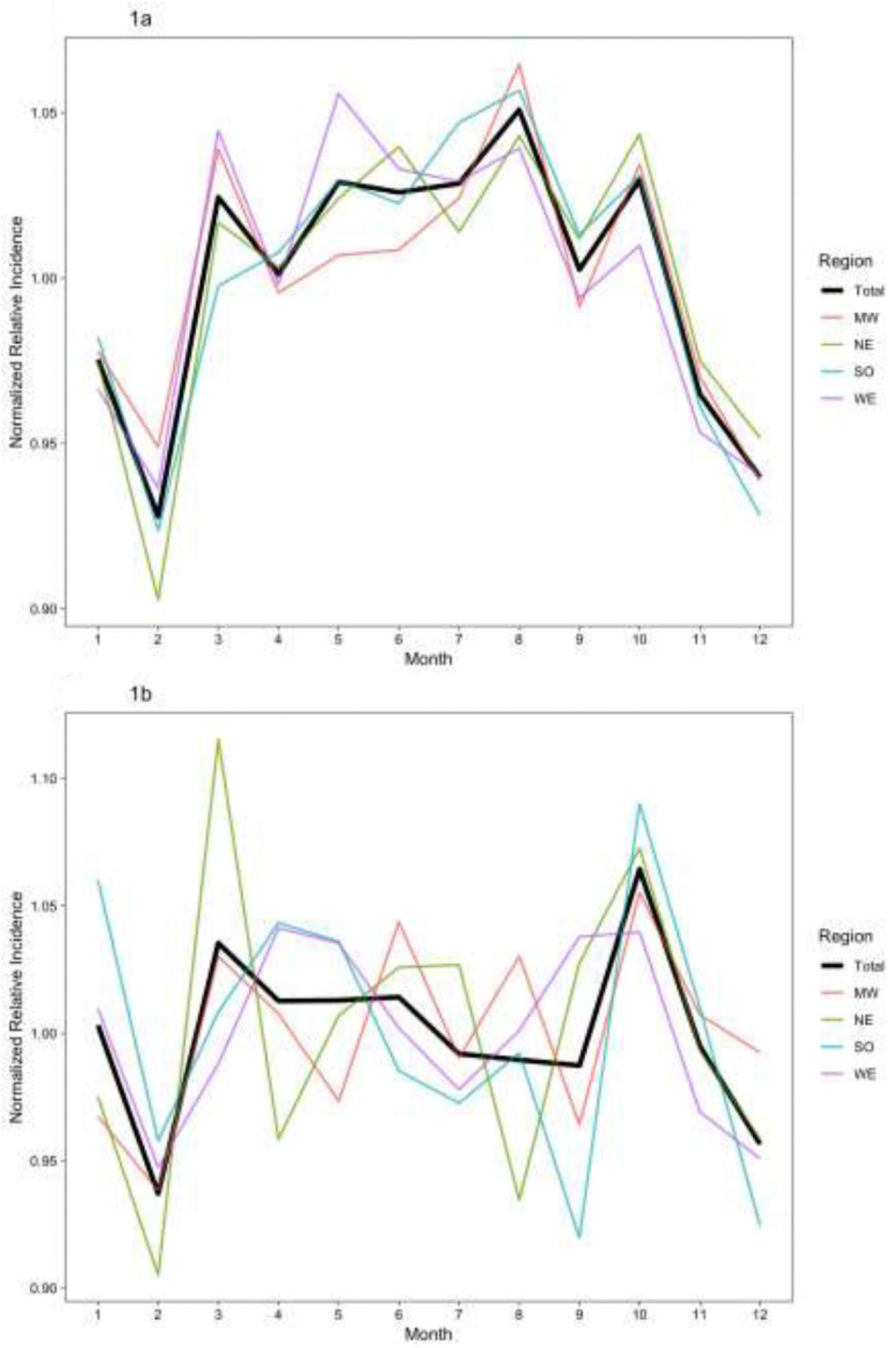

Figure 1 - Aggregate Time Series of HZ and HZO Codes, Normalized Time Series of Average Monthly Incidence Rate of HZ Codes from 2006–2017 by Region, Normalized to Total Patient Encounters

a.) Time series of normalized relative incidence for incident administrative codes for herpes zoster (ICD-9: 053.X and ICD-10: B02X) in the OLDW aggregated from 2006–2017. b.) Time series of normalized relative incidence for incident administrative codes for herpes zoster ophthalmicus (ICD-9: 053.2 and ICD-10: B023.X) in the OLDW aggregated from 2006–2017. For both a.) and b.) nationwide rates are shown in black and normalized to national total monthly patient encounters and scaled to normalized relative incidence as

described in the text. Regional rates are shown as colored (MW = Midwest, NE = Northeast, SO = South, WE = West) and each is normalized to its regional total monthly patient.