Letter to the Editor

Estimation of Incidence of Herpes Zoster in Three Cities of China, 2019–2020*

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Herpes zoster (HZ) is a painful condition resulting from reactivation of dormant varicella-zoster virus (VZV) in a previously VZV-infected person[1]. Typical clinical manifestation of HZ are unilateral radicular pain and a vesicular rash limited to one side of the body in the distribution of a nerve[2]. The most common complication of HZ postherpetic neuralgia (PHN), which occurs in 5% to 30% of HZ patients. PHN presents as severe, persistent pain that remains after the HZ rash has resolved[3]. Domestic studies found anti-VZV antibody seroprevalences of 95%-100% among individuals aged ≥ 30 years in China[4,5], indicating the near-universal, sizable pool of individuals at risk for HZ in China.

HZ is not a nationally notifiable condition in China, challenging population-based studies to estimate incidence of HZ. The availability of hospital-based electronic medical records makes it possible to estimate morbidity and complications through active surveillance studies. We used available electronic medical records to estimate HZ incidence in three cities in China during 2019–2020, extrapolating to the population level and analyzed clinical characteristics in three cities in China from 2019 to 2020 of HZ.

We selected a convenience sample of three non-provincial capital cities (Lu'an, Zibo, and Tongchuan). These cities were selected because they had relatively limited in-and-out population mobility, which could influence stability of incidence estimates. These cities experienced less stringent non-pharmaceutical interventions against COVID-19 during the study period, The population sizes of Lu'an, Zibo, and Tongchuan were 4.4 million, 4.7 million and 0.7 million respectively. We categorized all hospitals in the study setting according to data availability: those with full electronic medical record data, including clinical characteristics (Group A), those with only patient visit volume (Group B), and those for which only hospital type and level were known (Group C). We excluded specialized hospitals that lacked HZ case reports and did not provide care for HZ patients (orthopedic hospitals, stomatological hospitals, Tuberculosis control centers, and mental health centers) and personalized clinics. Supplementary Figure S1 (available in www.besjournal.com) shows hospital types and tiers in China.

Clinical data in Zibo was obtained from the electronic healthcare record database of the Zibo public health information platform, which integrates electronic medical records of all tier-2 and tier-3 hospitals and some primary hospitals in Zibo. Clinical data in Lu'an and Tongchuan were obtained from independent hospital information systems (HIS). The centers for disease control and prevention (CDCs) in the three cities determined hospital tier and type (Supplementary Figure S1).

In group A hospitals, we performed case searches with the terms, "Daizhuangpaozhen" "Daipao" "Daizhuang" "Chuanchuang", and "HZ" to identify HZ cases seen during the study period of January 1, 2019 to December 31, 2020. All diagnoses related to herpes zoster were included.

From group B hospitals in Zibo and Lu'an, we obtained data on the annual number of visits across the entire facility. The number of HZ cases was estimated by extrapolation of the group A hospital

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proportion of HZ cases to all patient visits during the same study year and at the same tier and type of hospital using the formula, total visits in group B hospitals × (number of HZ cases in same tier and type group A hospitals / total number of group A hospital visits). The number of HZ cases in Tongchuan group B hospitals was similarly extrapolated, but with the refinement that the number of visits was specific to clinical departments: number of visits in specific departments × (number of HZ cases in the corresponding department of group A hospitals of the same tier and type / the total number of visits in all relevant clinic departments during the same study month) (Supplementary Tables S1–S3, available in www.besjournal.com).

For group C hospitals that lacked visit volume data, we estimated HZ case numbers to be the average estimated number of cases in group A and B hospitals of the same tier and type with the formula: estimated number of cases in hospitals group A and B of the same tier and type / the number of hospitals A and B of the same tier and type.

Based on interviews of experts, the number of HZ cases in the village clinic was counted as 2 cases per year. For incidence estimates, population denominators were the resident populations reported in the seventh census.

Descriptive statistics were used to describe clinical characteristics of HZ cases from group A hospitals. We used χ^2 significance tests to compare categorical variables, and binary logistic regression models were used for multivariate analysis. Data analyses were conducted using Excel software (version Home and Student 2019, Microsoft Office, USA) and SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

This study was approved by the China CDC Ethical Review Committee (approval number 202123). Individual informed consent was not required or obtained for this study, which was based on electronic medical records.

In Lu'an, eight group A hospitals, 17 group B hospitals and 280 group C hospitals were included in the study; In Zibo, 23, 115, 141, respectively, were included. There were nine tier-2 and tier-3 hospitals in Tongchuan, all of which were included as group A hospitals, and Group A also included nine tier-1 hospitals. The remaining 51 tier-1 hospitals were included in group B hospitals. There were no group C hospital in Tongchuan. There were 2,806, 1,785, and 549 village clinics in Lu'an, Zibo, and Tongchuan, respectively. Using hospital system medical records and an incidence estimation method based on hospital type, tier, and data availability, we found that the incidence of herpes zoster in three cities in China was between 4.4 and 4.8 per thousand total population (Table 1). The highest incidence was among the older residents (Figure 1).

We found that the estimated incidence in Tongchuan was slight higher than that in the other two study cities. Because we were able to obtain diagnostic data of all HZ cases from January 2019 to December 2020 in all tier-2 and tier-3 hospitals in Tongchuan, the Tongchuan estimate may be the most accurate of the three estimates. Similar to our incidence estimates, two retrospective studies that used the Big Data Platform for Health Management in Yichang City, Hubei Province during 2016–2017 found an HZ incidence of 5.06 per 1,000 among urban residents. They also found that among > 50-year-olds and > 60-year-olds, incidences were 8 and 10 per 1,000 respectively[6]. A community-based retrospective study in Laiwu district, Jinan city, Shandong Province reported HZ incidence of 14 per 1,000 population among > 60-year-olds in 2018[7]. Differences in study design and data sources likely contributed to differences in the incidence estimates of these domestic studies.

We obtained diagnostic data of 19,196 HZ cases in the 49 group A hospitals (Supplementary Table S4, available in www.besjournal.com). The median (interquartile range, IQR) age was 55 (42, 66) years. 6.66% (1,279) cases had PHN. Among patients ≥ 50 years old, 8.03% had PNH. A retrospective study in 34 districts / counties in Guangdong Province found that 40.2% of the HZ cases among ≥ 50-year-olds had pain for more than one month after the onset of HZ rash[8]. In Yinzhou District (Zhejiang Province), 7.26% of HZ cases among ≥ 50-year-olds had pain more than 90 days after HZ onset[9]. PHN estimates in domestic studies vary significantly by study design, target population, and definition of PHN[9]. It is generally acknowledged that risk of developing PHN increases with age (Supplementary Table S5, available in www.besjournal.com).

Our study found around 22% HZ cases were under the age of 40 years, representing a relatively underappreciated burden of disease. Given the profound impact of HZ and its complications on physical and mental well-being and productivity, it is important to consider prioritizing prevention and management of HZ and associated complications in these younger adults. We also found that 52 infants had HZ. However, we did not investigate history of varicella during pregnancy in these 52 mothers,

Table 1. Estimated incidence (per 1,000 population) of HZ by City

Variables	Lu'an					Zibo					Tongchuan				
	Population	2019		2020		Annul Incidence	Population	2019		2020		Annul Incidence	Population	2019		2020		Annul Incidence
		cases	Incidence (‰)	cases	Incidence (‰)			cases	Incidence (‰)	cases	Incidence (‰)			cases	Incidence (‰)	cases	Incidence (‰)	
Gender																		
Male	2,257,483	8,965	3.97	9,865	4.37	4.17	2,359,559	10,254	4.35	11,598	4.92	4.63	355,376	1,771	4.16	1769	4.85	4.50
Female	2,136,216	9,793	4.58	10,379	4.86	4.72	2,344,579	10,653	4.54	12,068	5.15	4.85	342,946	1,477	5.16	1723	5.16	5.16
Age group																		
0–	2,025,518	3,920	1.94	3,746	1.85	1.89	2,038,421	3,973	1.95	4,184	2.05	2.00	315,680	419	1.33	452	1.43	1.38
40–	620,657	2,758	4.44	2,383	3.84	4.14	723,119	3,261	4.51	3,638	5.03	4.77	138,547	448	3.24	420	3.03	3.13
50–	81,487	4,783	5.88	5,645	6.94	6.41	849,441	4,710	5.55	5,736	6.75	6.15	93,016	844	9.08	895	9.62	9.35
60–	468,134	3,668	7.84	3,689	7.88	7.86	604,802	5,173	8.55	5,505	9.10	8.83	86,394	924	10.70	908	10.51	10.60
≥ 70	465,903	3,628	7.79	4,779	10.26	9.02	488,355	3,790	7.76	4,604	9.43	8.60	64,684	613	9.47	817	12.63	11.05
Total	4,393,699	18,758	4.27	20,244	4.61	4.44	4,704,138	20,907	4.44	23,666	5.03	4.74	698,322	3,248	4.65	3492	5.00	4.83

Note. HZ, Herpes Zoster; Population is the resident populations reported in the seventh census.

which should be a topic for further study to understand the pathogenic mechanisms underlying such occurrences (Supplementary Table S4). Most likely, these represent reactivation of dormant VZV from intrauterine fetal infections.

A strength of our study is that we developed a method to estimate population incidence of a non-notifiable condition. We categorized all hospitals in the study setting into three groups. Estimates for hospitals without full clinical data were extrapolated from estimates from hospitals with full clinical data based on visit volume and adjusted for level and type of hospital to obtain population-based estimates of incidence. Our study certainly has several limitations. Group A hospitals were not a random sample of hospitals, and the method we used for weighting the estimated the number of cases in hospitals group B and hospitals group C may introduce bias. Second, we did not make estimates of HZ case numbers in personal health clinics and among individuals who did not seek medical attention, and this will lead to underestimating the incidence of mild HZ cases. Thus, our results can only represent medically-attended HZ. However, these cases are most severe and are policy-relevant. The phenomenon of finding only the medically-attended cases is similar to a novel surveillance strategy for bacterial meningitis that was also hospital-based[10]. Third, the three cities we studied were a convenience sample and cannot be considered as representative of all of China. Although the age-based incidence may vary across China, the similarity of our incidence estimates in the three cities provides some reassurance that all-China results would likely be similar to our findings. Future studies could use the methodology we developed to estimate age-based incidences in other areas to assess generalizability of incidence rates.

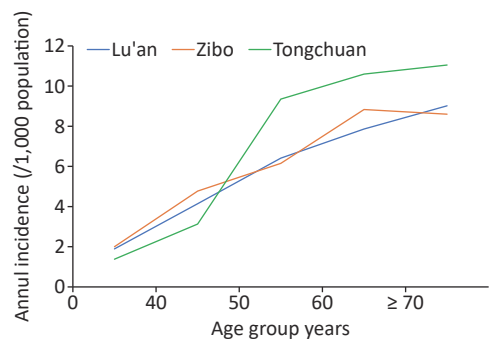

Figure 1. Annual incidence of HZ by city and age group during 2019–2020. HZ, herpes zoster.

In conclusion, our study showed that there is a significant burden of medically-attended HZ in China, with an overall incidence of about 4.5 cases per 1,000 total population. Elderly people are at greatest risk of HZ and PHN. Our study provide a methodology to estimate population incidence of non-notifiable conditions.

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