Epidemiology of herpes zoster among adults aged 50 and above in Guangdong, China

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Herpes zoster (HZ) exists widely in China and most cases occur among old people, but no epidemiology information of HZ was available. We aimed to investigate the epidemiology characteristics of HZ among adults aged 50 and over in Guangdong, China. A total of 34 counties/districts were randomly selected in Guangdong, and 7149 residents aged 50 and over were investigated by local CDC professionals using accidental sampling method. There were 247 respondents having had HZ before; the lifetime prevalence of HZ among people aged 50 and above in study area was 3.46%. The prevalence in females was higher than that in males. Pearl River Delta had the highest prevalence (5.29%), while Northern Guangdong had the lowest (1.87%). The annual incidence in the year 2013, 2012 and 2011 was 5.8, 3.4 and 4.1 per 1000 person-years, respectively. Detailed investigation of HZ cases showed that all cases meted the definition of HZ and had at least 1 typical symptom. 40% cases had suffered post-herpetic neuralgia. 75.9% cases had sought aid from hospital and 9.1% of them had been hospitalized. People who sought aid from hospital had more serious level of neuralgia. The epidemiology features of HZ in Guangdong were consistent with the current findings in other countries. The results of this study can provide baseline epidemiology information of HZ for further studies.

Introduction

Herpes zoster (HZ) and varicella both are caused by varicella zoster virus. The virus usually stays in the body in a dormant (inactive) state after a person recovers from varicella. The latent virus may be reacted when the body resistance is low and causes HZ, which is characterized by unilateral radicular pain and a vesicular rash, and the symptom is generally limited around one side of the body. The most frequent debilitating complication of HZ is post-herpetic neuralgia (PHN), 2,3 a neuropathic pain syndrome that persists or develops after the vesicular rash has healed. For most patients, the pain resolves relatively quickly in the weeks after the rash resolves, but in some patients (especially in elder people), the pain persists for months and years, profoundly affecting quality of life. 4

Herpes zoster exists all over the world, but the studies of its epidemiology were mainly reported in USA and Europe. The estimated annual number of HZ cases in the United States was about 1 million and almost one third of the general population will experience HZ, and half of the HZ patients older than 60 will develop PHN. In Europe, the incidence of HZ varied by countries from 2.0–4.6/1000

person-years and the incidence among people over 50 years old (>7/1000) was significantly higher than young people (<4/1000).^{6,7} Almost 2-thirds of HZ cases occurred in individuals aged 50 years or over.⁸

HZ also exists widely in China, but the studies about HZ mainly concentrated in diagnosis, therapy and other clinical aspects with limited epidemiological information. ^{9,10} HZ is not a notifiable infectious disease in China Many hospitals have established their own medical record system, but the information is isolated and of different format and quality. It is hard to get the epidemic information of HZ based on infectious disease reporting system or medical record system. Population based survey is an appropriate method to obtain more accurate epidemic information of HZ in China.

Guangdong locates in the southeast of China. It has a population of over 100 million people which account for nearly 7% of the national population. The proportion of population aged 65 and over is 7%, which is still in constant growth. The rapidly aging population and unbalanced social-economic development makes Guangdong just like a microcosm of Mainland China. As HZ mainly occurred in old people, the rapidly aging population may make the burden of HZ more serious in the future.

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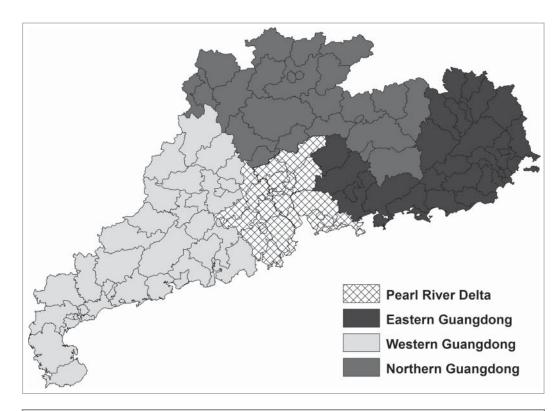


Figure 1. Four geographical regions of Guangdong Province.

We conducted a multi-stage sampling cross-sectional survey to investigate the epidemiology of HZ among people aged 50 and over in Guangdong, China. The results of this study can provide baseline epidemiology information of HZ for further studies.

Results

The epidemiology of HZ

A total of 7149 individuals (the designed sample size was 7140) were investigated in 34 sampled counties/districts, which were all residents of Guangdong and Yellow race. 247 of them reported to have HZ before the survey. The lifetime prevalence of HZ among people aged 50 and over in Guangdong was 3.46% (**Table 1**). The prevalence in female was higher than that in male (3.94% versus 2.86%, $\chi^2 = 6.103$, P = 0.013). The prevalence increased with age and the trend was statistically significant (the χ^2 of trend test was 12.802, P < 0.001).

(Fig. 1). The age distribution of the sampled population in these regions was (Table 2) balanced accordant with the demographic data of Guangdong province from statistical bureau. 12 The lifetime prevalence of HZ in different regions were of statistical significance ($\chi^2 = 32.218$, P < 0.001), Pearl River Delta had the highest prevalence while Northern Guangdong had the lowest (Table 3).

There were 4 geographical regions in Guangdong

Annual incidence in the year 2011, 2012 and 2013 ranged from 3.4 to 5.8 per 1000 person-years. The annual incidence had no statistical significant difference among different years (Table 4).

The characters of HZ cases

Eighty seven cases whose onset time was after 2011 reported their detailed clinical symptoms. All cases meted the definition of HZ and had at least 1 typical symptom. The proportion of having each typical symptom (vesicular rash, erythema and neuralgia) was about 90%, respectively. For 80% cases, the symptom was only limited around one side of the body. The symptom most commonly occurs on chest and back (46.0%), followed by waist and abdomen (43.7%). Arms and legs were rarely involved (8.0%) (Table 5).

Among 80 cases who had neuralgia, 56.3% lasted within one month, 30.0% lasted 1-3 months and 13.8% lasted more than 3 months. The incidence rate of post-herpetic neuralgia (neuralgia lasted over one month) was 40.2% (35/87). 75.9% (66/87) cases had sought consultation from hospital, 60 of them only visited out-patient clinic, and 6 of them were hospitalized. Mann-Whitney Test was used and found that people who sought consultation from hospital had more serious level of neuralgia (Z = -2.385, P = 0.017). More details were listed in Table 6.

Table 1. Lifetime prevalence (%) of HZ in different age and gender stratification

Age group	Male			Female			Total		
	Cases	Subjects	%	Cases	Subjects	%	Cases	Subjects	%
50 ~	23	1085	2.12	54	1542	3.50	77	2627	2.93
60 ~	36	1247	2.89	49	1374	3.57	85	2621	3.24
70 ~	17	602	2.82	25	627	3.99	42	1229	3.42
80 ~	16	278	5.76	27	394	6.85	43	672	6.40
Overall	92	3212	2.86	155	3937	3.94	247	7149	3.46

Table 2. Age distribution of the sampled population in different regions

	Age group					
Regions	50~ (%)	60∼ (%)	70 ~ (%)	80∼ (%)	Total	
Pearl River Delta	677 (35.1)	762 (39.5)	329 (17.1)	159 (8.3)	1927	
Eastern Guangdong	603 (36.0)	629 (37.5)	273 (16.3)	172 (10.3)	1677	
Western Guangdong	851 (37.6)	762 (33.7)	412 (18.2)	237 (10.5)	2262	
Northern Guangdong	496 (38.7)	468 (36.5)	215 (16.8)	104 (8.1)	1283	
Overall	2627 (36.7)	2621 (36.7)	1229 (17.2)	672 (9.4)	7149	

Discussion

This is a multi-stage sampling study, the study areas was selected randomly according to the systematic sampling method. Although the respondents were selected by non-random method (accidental sampling), the equilibrium of gender and age proved that this study was of good representativeness and could reflect the overall epidemiology situation of HZ in Guangdong.

It is generally easy to diagnose HZ based on the history and the clinical examination that shows the characteristic pain, grouped vesicular rash in a dermatomal distribution. HZ is a disease that would hardly be forgotten by the patients. The case definition in this study was clear and easy to be understood by respondents. Investigators not only explained the detailed symptoms, but also showed the photos of classic signs to respondents. These can ensure the collected information was of good quality. For nearly 25% of the respondents, the occurrence of HZ was based on their own judgment if they didn't go to a hospital, which may cause some concern of this study.

The lifetime prevalence of the symptomatic HZ (aged over 50) was 3.46%. In Taiwan, the previous HZ onset proportion during the latest 7 years was 3.43%. One study in North Carolina found a prevalence of 4.5% among blacks and 16.1% in whites. We found females were more susceptible to HZ than males in this study, which was consistent with the findings of most studies. 6,7,13

We observed that the lifetime prevalence differs in different areas of Guangdong, with higher in Pearl River Delta and lower in northern Guangdong. This regional difference may be attributable to several reasons. The surveillance data of varicella collected by Guangdong CDC pointed out that the incidence of

Table 4. Annual incidence of HZ in the year 2011, 2012 and 2013

Year	Cases	Annual incidence (1/1000 person-years)	95% CI (1/1000 person-years)
2011	29	4.1	(2.6,5.6)
2012	24	3.4	(2.1,4.7)
2013 [*]	34	5.8	(3.8,7.7)
Total	87	4.3	(3.4,5.2)

^{*}From January to October

varicella was higher in Pearl River Delta than other regions, so more people had been infected by varicella zoster virus and had the possibility to develop HZ. On the other hand, psychological stress had been proved to be a critical risk factor of HZ. ^{15,16} People in Pearl River Delta generally have greater psychological stress than other areas. ^{17,18}

The annual incidence rate of HZ among people over 50 years old in Guangdong was 3.4–5.8 per 1000 person-years. It was comparable with the result of UK (about 5 per 1000 person-years), ¹⁹ and lower compared with the incidence of HZ in Taiwan (6–12 per 1000 person-years), ¹³ Boston (5–12 per 1000 person-years), ⁴ France (8.99 per 1000 person-years)²⁰ and Germany (9.80 per 1000 person-years). ²¹ These differences may attribute to race distribution. It had been proved that the risk of developing HZ differs dramatically in different races and whites have significantly higher risk than blacks. ¹⁴ We found that 40.2% patients had PHN one month after the onset of the zoster rash. In the United States, and Taiwan, the percentage among old people was about 50%, ⁵ 31.2%, ¹³ respectively.

It has been widely reported that the most common onset body area of HZ were chest and back (over 50%), followed by waist and face. The symptoms were usually limited around one side of the body. It is consistent with the symptom characters of reported HZ cases in this study. The definition of HZ cases and self-reporting quality was also proved to be appropriate in this study.

In this study, 17.2% (15/87) of cases reported having bilateral symptoms, this proportion was a little higher. We found 66.7% (10/15) of them with onset time in the year 2011, so this may due to recall bias. 16.1% (14/87) of cases reported having multiple localization, in which 57.1% (8/14) multiply

Table 3. Lifetime prevalence (%) of HZ in different regions

	Male			Female			Total		
Regions	Cases	Subjects	(%)	Cases	Subjects	(%)	Cases	Subjects	(%)
Pearl River Delta	30	747	4.02	72	1180	6.10	102	1927	5.29
Eastern Guangdong	23	795	2.89	35	882	3.97	58	1677	3.46
Western Guangdong	33	1055	3.13	30	1207	2.49	63	2262	2.79
Northern Guangdong	6	615	0.98	18	668	2.69	24	1283	1.87
Overall	92	3212	2.86	155	3937	3.94	247	7149	3.46

⁻Pearl River Delta: Guangzhou, Shenzhen, Dongguan, Foshan, Zhongshan, Zhuhai, Jiangmen

⁻Eastern Guangdong: Shantou, Chaozhou, Meizhou, Jieyang, Shanwei, Huizhou

⁻Western Guangdong: Zhanjiang, Maoming, Yangjiang, Yunfu, Zhaoqing

⁻Northern Guangdong: Shaoguan, Qingyuan, Heyuan

Table 5. The symptom characters of HZ cases

		No (%)	Yes (%)	Can't remember (%)	Total
Symptom	vesicular rash	7 (8.0)	79 (90.8)	1 (1.1)	87
	erythema	8 (9.2)	77 (88.5)	2 (2.3)	87
	neuralgia	6 (6.9)	80 (92.0)	1 (1.1)	87
Body part	both sides of the body	70 (80.5)	15 (17.2)	2 (2.3)	87
	chest and back	47 (54.0)	40 (46.0)	0 (0)	87
	waist and abdomen	49 (56.3)	38 (43.7)	0 (0)	87
	head and face	77 (88.5)	10 (11.5)	0 (0)	87
	neck	78 (89.7)	9 (10.3)	0 (0)	87
	arms and legs	80 (92.0)	7 (8.0)	0 (0)	87

located on "chest and back" and "waist and abdomen." It is hard to differentiate these 2 parts of the body, it is reasonable that some subjects reported having symptoms on this 2 body parts. We found that people who sought consultation from hospital had more serious level of neuralgia. Many studies^{23,24} had pointed out that neuralgia was the most intolerable symptom of HZ, it is reasonable that patients with neuralgia were more likely to see doctor.

The prevalence of PHN in this study was 40%. The existing studies pointed that the risk of developing PHN varied from 5% to more than 30%. The reason may mainly due to 2 aspects.

The first reason was that the population of this study was over 50 years old. Previous study⁵ has pointed out that 50% of patients older than 60 who have HZ will develop PHN, and up to 75% of those over 70 will suffer from this complication. Old people with HZ were more likely to develop PHN. The second reason may due to recall bias. As data were collected retrospectively, people with neuralgia may not remember the exact lasting time. The intolerable pain of neuralgia may strengthen their memory of the suffering time.

Several limitations were needed to be mentioned in this study. Study areas were randomly selected but the respondents were accidentally selected. The representativeness of the population needed to be considered. We adopted the idea of quota sampling to keep the equilibrium of gender and age in order to reach good representativeness. The demographic distribution of the selected study sample was proved to be accordant with the demographic data of Guangdong province from statistical bureau. ¹² For many respondents who didn't have clinical diagnosis before, the history of HZ was judged by the respondents' own interpretation based on the explanation and classic photos of symptoms given by investigators. This may bring some reporting bias and recall bias, but the bias was proved to be minor as 99.7% of respondents can clearly recall if he/she ever had HZ before (only 0.3% answered

"unknow") and the self-reported symptom characteristics were consistent with clinical manifestation.

In United States, The HZ vaccine was recommended for people aged 60 years and older by the Advisory Committee on Immunization Practices (ACIP) in 2006 to reduce the risk of HZ and its associated pain. A cohort study was conducted and found the HZ incidence rate was 10.0 per 1,000 person-years among unvaccinated participants and 5.4 per 1,000 person-years among vaccinated participants. Vaccine effectiveness against HZ was 48%. HZ vaccine has not been introduced into Mainland China. This study can provide baseline epidemiology information of HZ before the initiation of related clinic trials.

In summary, the epidemiology features of HZ in Guangdong were consistent with the current findings of other regions. The introduction of HZ vaccine is needed to be concerned to reduce the disease burden of HZ.

Material and Method

Study design

The estimation of the lifetime prevalence of the symptomatic HZ in the population was the primary purpose of the survey. Sample size was calculated based on Formula 1, in which p was the estimated lifetime prevalence of HZ (3.4% was used according to the result of Taiwan¹³), δ was the permissible error (0.05%) and α was the significant level (5%).

$$n = \left(\frac{\mu_{\alpha/2}}{\delta}\right) p(1-p)$$
 Formula 1

n was 5048 after primary calculation. Considering the effective response rate was about 70% and the sample size should be

Table 6. The relation between occurrence of neuralgia and medical consultation

		Have neuralgia				
Seen in hospital	<1 month (%)	1-3 month (%)	≥4 month (%)	Have no neuralgia	Can't remember (%)	Total
Yes	33 (50.0)	20 (30.3)	10 (15.2)	2 (3.0)	1 (1.5)	66
No	12 (57.1)	4 (19.0)	1 (4.8)	4 (19.0)	0	21
All	45 (56.3)	24 (30.0)	11 (13.8)	6 (6.9)	1 (1.1)	87

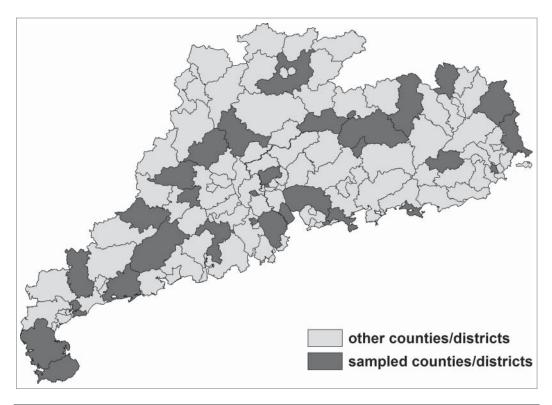


Figure 2. Sampled counties/districts in Guangdong Province.

divided equally into 170 villages/streets, the total sample size was finally set to 7140.

There are a total of 126 counties/districts in Guangdong Province. Systematic sampling method was used to select 34 counties/districts based on administrative code (Fig. 2). Five villages/streets were then randomly selected in each county/district. In each village/street, 42 subjects over 50 years old were investigated using accidental sampling method. The sample size was 210 in each county/district and 7140 in the whole province. Our survey began on October 28, 2013. This study was conducted by Guangdong provincial Center for Disease Control and Prevention (GDCDC).

Survey implementation

Two investigators (one from provincial/municipal CDC and one from local CDC) were engaged in the survey in each village/street. They went into different households and visited people who meet the requirements (over 50 years old and residents in Guangdong) accidentally. We accepted the idea of quota sampling. Gender and age stratified $(50\sim, 60\sim, 70\sim)$ equilibrium were considered during the investigation process in each village/district. The investigation of one village/street could be finished when its sample size reached 42.

Three questions would be asked for each eligible respondent (gender, age and if he/she ever had symptoms of HZ or was diagnosed as HZ by a doctor). The investigators would explain to the respondents what the typical symptoms of herpes are and showed the typical photos of signs. The case definition for reporting was based on the website of American CDC²⁸ and was confirmed by

clinic expert of Skin Disease Hospital of Guangzhou to make it easily understood. The typical symptoms were defined as "grouped vesicular rash or erythema that appeared in a dermatomal distribution, generally limited around one side of the body (unilateral distuibuted) and usually accompawith unilateral radicular itching or pain." The lifetime prevalence of HZ was then calculated.

Once the respondent's onset time was within 3 years before this study (since 2011), a detailed questionnaire interview would be conducted to collect the information about the symptoms (including onset body areas, whether had post-herpetic neuralgia and the lasting time) and treatment (whether had come

to the hospital and the hospital's level). According to the new onset cases of HZ during the fixed time period (from 2011 to 2013), the incidence of HZ could be estimated base on Formula 2.

Annual incidence (person – year)

 $= \frac{\text{occurrence during the fixed time period}}{\text{total observed person} - \text{year in the fixed time period}}$

Formula 2

The definition of HZ and photos of typical symptoms used in this study was confirmed by clinical experts of dermatological department. The design of the survey, the implementation process and the content of questionnaire were also determined after the argumentation of epidemiology experts in GDCDC and professor from the School of public health in Guangdong Pharmaceutical University.

Ethical approval and informed consent

Approval to conduct this study was granted by the relevant departments of GDCDC. All information was collected after the permission of the participants. Verbal informed consent was sought from each participant. Investigator would explain that their information would be only used to estimate the prevalence of HZ.

Pilot survey

We conducted a pilot survey in Foshan city before the formal survey. Two investigators visited 35 people who meet the inclusion criteria. After the explanation of the definition of HZ

and the display of photos, all respondents can clearly recall if he/she ever had HZ before. Though no HZ related case was found during this pilot survey, the survey process was proved to be effective and the result was reliable.

Data analysis

The lifetime prevalence of HZ was calculated. Subgroup analysis was taken under different gender, age and regional stratification. Chi-square test was used to find if the differences were of statistical significance between groups. Considering old people may not clearly recalled the specific onset year if the time interval is very long, we set the cut-off point of "year 2011" when estimate the incidence of HZ to reduce recall bias. Annual incidence of HZ in the year 2011, 2012 and January to October in 2013 were calculated. The characteristics of clinical manifestation and post-herpetic neuralgia were analyzed for the cases occurred after 2011.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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