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Research Article

Meta-Analysis of the Trend of Varicella Zoster virus Seroprevalence with Age in China

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Abstract

Background: Varicella-Zoster Virus (VZV) is the pathogen of human varicella and herpes zoster, its prevalence is related with the host's immune response and the seropositivity rate of VZV-immunoglobulin G (IgG) antibodies in the general population. The aim of this meta-analysis was pooled on the comprehensive information of the epidemiology of VZV infection and analyzed the seropositivity of VZV-IgG antibodies in different age groups, gender, and regions in China, so as to arouse people's attention on VZV.

Methods: We performed a systematic review by searching both English and Chinese literature databases. Random or fixed effects models were used to summarize the prevalence of VZV according to statistical tests for heterogeneity. Subgroup, sensitivity, and meta-regression analyses were performed to address heterogeneity. Publication bias was evaluated using Egger's test. Results: 2035 literatures were obtained by searching keywords "seroprevalence", "varicella zoster virus" and "VZV-IgG antibodies". Literatures were screened according to the inclusion criteria and 10 studies from 1997 to 2019 with a total of 9166 individuals were included. According to the results of heterogeneity test, random effect model and fixed effect model were used for system analysis. The heterogeneity was calculated using I-square statistics.

Results: The overall VZV seroprevalence in the Chinese population was 57.1% (95% CI:45.3% - 68.5%), and the peak prevalence was 93.37% (95% CI: 90.7%-95.7%)in the age 36-45while the VZV seroprevalence rate (84.7%, 95% CI: 48.8% - 100%) was not increased in individuals of45 and older.

Conclusion: The prevalence of VZV increases with age, and there was no significant difference between different genders orregions. This results can provide epidemiological evidence for the prevention and treatment of VZV.

Keywords: Age Stratification; China; Seroprevalence; Trend; Varicella-Zoster Virus

Background

Varicella-Zoster Virus (VZV) is the pathogen of human varicella and herpes zoster, and humans are the only host [1]. An average of 4.2 million severe varicella cases cause hospitalization or death worldwide each year [2]. The prevalence of herpes zoster is very high in China, and it related to the age [3]. VZV prevalence varies from country to country, ranging from 2.0 to 4.6/1,000 person/year, without obvious geographic trend [4,5]. VZV is highly infectious and usually transmitted by respiratory droplets. Chicken pox is more common in children, while herpes zoster is more common in adults. Advanced age and dysfunctional cell-mediated immune responses are two well-established risk factors for VZV reactivation [6]. Complications, however, do occur, particularly in infants, pregnant women, and in immunocompromised individuals, including Post Herpetic Neuralgia (PHN) [7]. The prevalence of VZV is closely related to season and climate. Spring and autumn are high-risk seasons. The prevalence of VZV in tropical climates is low, but the average age of VZV infection is higher [8,9]. Europe, America, Japan, Korea, and China have adopted immunization strategies to control the epidemic of VZV through vaccination. In the sero-epidemiological investigation of VZV, Enzyme-linked immunosorbent assay (ELISA) is usually used to detect the concentration of varicella-zoster virus antibody (VZV-IgG) in serum. The concentration of VZV-IgG (> 100 mIU/mL) is positive, which indicates that the subjects have the ability to resist varicella virus infection.

With the immunity of the elderly decreasing, they are more susceptible to virus infection, so that VZV prevalence increases and VZV would bring serious economic and spiritual burden to society. The purpose of this study was to investigate the seroprevalence of VZV in the general population, analyze the influencing factors of VZV infection, and provide a theoretical basis for the prevention and treatment of VZV.

Materials and Methods

Search strategy

Studies on the immune epidemic of varicella-zoster, which were published in the last 30 years in China, were searched on PubMed,

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the China National Knowledge Infrastructure (CNKI) database, WANFANG database, and the Chinese Scientific Journals Full-Text Database (CQVIP. Chinese and English search terms included "Varicella-zoster virus", "varicella", "Herpes zoster", and "Varicella immunity". The list of all eligible studies and reviews was manually scanned to identify additional studies for inclusion. During extraction of publications, we avoided subjective bias by omitting names o011f the authors, journals, year, and country.

Inclusion Criteria

All cross-sectional studies which focused on VZV seropositivity in the Chinese population were included. Of the total publications, duplicate and similar ones were identified and excluded. Since both English and Chinese publications were included, publications with same data but different languages were removed in the next step. The title and abstract of the retrieved studies were independently screened by two investigators, and the full texts of the selected studies were further evaluated according to the eligibility criteria. Any disagreements were resolved by consensus after consultation with a third reviewer. Inclusion criteria: (1) the Chinese and English studies on varicella-zoster virus immunization epidemics in different regions of China; (2) the literature has obvious age stratification; (3) the subjects are from the general population; (4) VZV seroprevalence of the population investigated in the literature. Exclusion criteria: any study that did not contain this information was excluded.

Data Extraction and quality assessment

Two evaluators independently retrieved documents and extracted data. Information about the study design, eligible population, age, and gender distribution, and inclusion and exclusion criteria were checked. When they disagreed, they could solve the problem by discussion or by soliciting opinions from third parties. Firstly, the data of all studies were extracted, and the age stratification interval was determined. The data was pooled according to age stratification (1-3, 4-6, 7-13, 14-19, 20-35, 36-45, > 45) by Microsoft Excel spreadsheet. The total prevalence, 95% confidence interval (CI; Lower-Upper CI) and estimate were analyzed and calculated by open-meta-analysis software. Forest plots were drawn by R 3.6.0, GraphPad Prism, open-meta-analysis, and RevMan 5.3 software. Two researchers independently assessed the quality of each included study using observational study criteria that were recommended by the Agency of Healthcare Research and Quality. Only when two reviewers agreed was the study included in the meta-analysis. The retained articles were required to have a quality score.

Statistical Method

RevMan 5.3, R 3.6.0, GraphPad Prism and open-meta-analysis software was used for meta-analysis. The heterogeneity of the included studies was tested by chi-squared (χ^2) test. The heterogeneity was determined by I^2 value, and I^2=0 was considered indicative of the variation between studies that was only caused by sampling error. I^2<0.5 was considered indicative of a lack of significant heterogeneity among the included studies, and a fixed-effects model was used for analysis. I^2>0.5 was considered indicative of substantial heterogeneity and a random-effects model was used for analysis. Meta-analysis results are represented by forest plots [10]. Prevalence estimates and 95% CI (Lower CI-Upper CI) were calculated using open meta-analysis software. Confidence areas were also calculated in R 3.6.0. Additionally, sensitivity analysis was performed to assess the influence of any particular study on the pooled estimate.

Publication bias was evaluated using Egger's Test, and independent t-tests were performed as appropriate. The significance level was set at a *P*-value of less than 0.05.

The Ethics Committee of the First Affiliated Hospital of Xian Medical University approved the study.

Results

Literature Retrieval Results

By searching PubMed, CNKI, WANFANG, and CQVIP databases, 2,035 papers were obtained. By eliminating duplicate papers, 63 papers were preliminarily obtained through reading topics and abstracts in CNKI (n=21), PubMed (n=39), and other methods (n=3). Thirteen incomplete studies and 35 papers without age stratification were excluded by acquiring and reading the full text. When compared with the age stratification criteria, 5 studies were excluded. According to the inclusion and exclusion criteria, 10 studies [11-20] were included in the meta-analysis. 9166 individuals in China were included. A flowchart depicting the screening process of references at each stage is shown in figure 1.

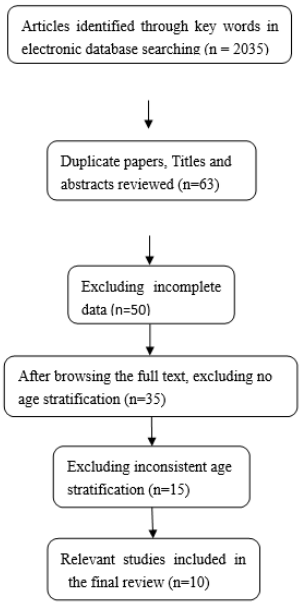

Figure 1: The flow chart of study screening.

Basic Information of Included Studies

The level of VZV antibodies in a healthy Chinese population was studied in 10 papers, from which the research data was collected from 1997 to 2019. The subjects were surveyed from 10 provinces in different geographical regions in China (Shanghai, Guangdong, Beijing, Liaoning, Sichuan, Heilongjiang, Fujian, Zhejiang, Henan, and Jiangsu), involving healthy children, residents and rural populations. Eleven thousand six hundred sixty-six individuals were included in this cross-sectional study. The sample size of each study ranged from 114 to 3076. There was no gender difference, and the age of subjects was between 1 and 70 years old. Enzyme-linked immunosorbent assay (ELISA) was used to detect anti-VZV-IgG antibodies in serum. The basic information of included studies is shown in table 1.

First Author	year of collection	Region	Target population	Prevalence of seropositivity in age groups positive seroprevalence/sample size (%)							Total	Score
				1 - 3	4 - 6	7 - 13	14 - 19	20 - 35	36 - 45	>45		
Cao Huilin [11]	1997	Shanghai, Beijing, Dalian, Guangzhou, Chengdu	City Residents	79/495 (15.96)	252/505 (49.90)	356/509 (69.94)	449/513 (87.52)	519/560 (92.68)	460/494 (93.12)	NA	2155/3076 (70.06)	9
Wang Wen [12]	2004	Shanghai, Dalian, Guangzhou, Chengdu	Healthy people	74/393 (18.83)	211/405 (52.10)	280/409 (68.46)	354/411 (86.13)	410/447 (91.72)	366/400 (91.50)	NA	1695/2,465 (68.76)	8
Li Xikun [13]	2016	Haerbin	Healthy people	159/240 (66.25)	296/396 (74.75)	253/364 (69.51)	152/203 (74.88)	NA	NA	NA	860/1203 (71.49)	9
Pan Weiyi [14]	2003	Fujian	City/Rural Residents	8/58 (13.80)	19/56 (33.90)	NA	NA	NA	NA	NA	27/114 (23.7)	9
Dong Yanhong [15]	2016	Chaoyang District of Beijing City	Healthy people	NA	NA	NA	NA	NA	78/80 (97.50)	192/200 (96.00)	270/280 (96.40)	8
Wu Xiaohong [16]	2015	Jinhua	Healthy people	NA	65/180 (36.11)	NA	NA	NA	NA	NA	65/180 (36.10)	9
He Xin [17]	2011	Luohe	Healthy people	23/34 (67.65)	26/39 (66.67)	24/40 (60)	NA	NA	NA	69/102 (67.65)	142/215 (66.00)	7
Zhou Hua [18]	1998-2001	Shanghai	Healthy people	51/283 (18.02)	93/307 (30.29)	NA	NA	NA	NA	NA	144/590 (24.4)	7
ZhengGuanzeng [19]	1998	Taizhou, Hangzhou	Healthy people	10/77 (12.99)	37/268 (13.81)	261/420 (62.14)	NA	NA	NA	NA	308/765 (40.30)	8
GuoXue [20]	2007	Maoming City	Rural children	NA	NA	53/139 (38.13)	117/139 (84.17)	NA	NA	NA	170/278 (61.15)	8

Table 1: Basic information for included studies.

Prevalence of VZV

Data were collected from 10 studies according to age stratification (1-3, 4-6, 7-13, 14-19, 20-35, 36-45, and > 45) and gender. Prevalence estimates and 95% CI (Lower CI-Upper CI) were showed in table 2. VZV prevalence in different age groups are shown as a forest plot in figure 2. At the ages of 1–3, 28.38% (95% CI: 14.4%-44.8%) of children were shown to be infected. The seropositivity rate of VZV-IgG antibody sharply increased from 43.37% (95% CI: 30.0%-57.3%) at the age of 4-6 to 69.73% (95% CI: 64.3%-74.9%) at the ages of 7-13. The peak prevalence was seen in the age group of 36-45 at 93.37% (95% CI; 90.7%-95.7%), while the VZV seroprevalence rate (84.7%, 95% CI: 48.8%-100%) was not increased in individuals aged 45 and older. The trend of age-stratified VZV seroprevalence rates in the Chinese population from 1997 to 2019 is shown in figure 2.

Ten studies explored the seropositivity rate of VZV antibody, and the estimated values of VZV prevalence and 95% confidence intervals in each study were calculated and pooled. Due to substantial heterogeneity, a random effect model was performed in the meta-analysis. The overall VZV seroprevalence in the Chinese population was 57.1% (95% CI; 45.3%-68.5%). The results showed that 5796 individuals out of 9166 were seropositive for anti-VZV-IgG antibody (Figure 3).

Seven studies observed the prevalence of anti-VZV antibodies in different sexes, The results suggested that the prevalence of VZV in man was slightly higher than that in woman, with no statistical significance (P>0.05) (Figure 4).

Sensitivity analysis

Two citations had a quality score of 7, the lowest among the included studies. In the sensitivity analysis, we noticed a slight change

Age group	Estimate	95% CI (lower CI-upper CI)	N of studies	Total sample	I^2(%)	P
1-3	28.38%	(0.144-0.448)	8	1580	97.6%	<0.01
4-6	43.37%	(0.300-0.573.)	9	2295	98%	<0.01
7-13	69.73%	(0.643-0.749)	6	1881	82%	<0.01
14-19	83.48%	(0.765-0.894)	3	1127	88%	<0.01
20-35	92.26%	(0.905-0.938)	2	1007	0%	0.569
36-45	93.37%	(0.907-0.957)	3	974	51%	0.130
>45	84.70%	(0.488-1.000)	2	302	98%	<0.01

Table 2: Prevalence estimates and 95% confidence intervals (CI) in different age groups.

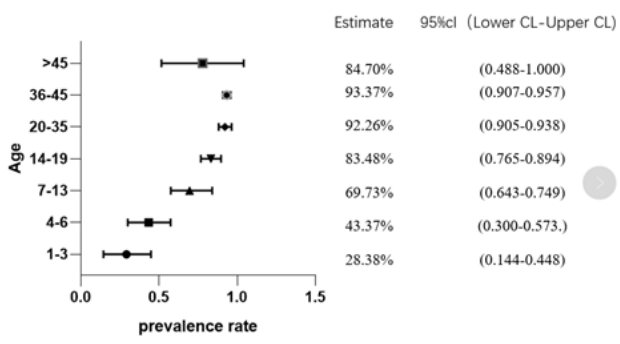

Figure 2: Varicella immunization forest plots at different age levels (prevalence estimate).

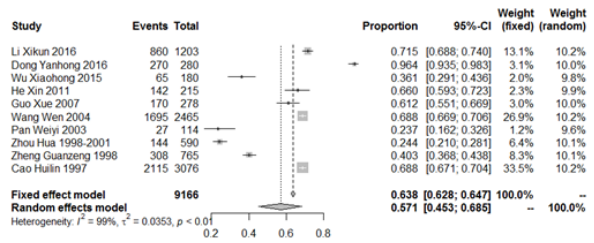

Figure 3: Forest plots of VZV prevalence in each study.

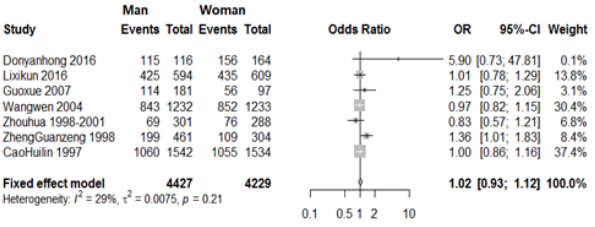

Figure 4: Forest plots of VZV prevalence in different genders.

in the pooled prevalence estimate (from 51.4 to 60.9 %) when we omitted these 2 studies (Figure 5). Egger's linear regression test (P=0.322) suggested no significant publication bias (Figure 6).

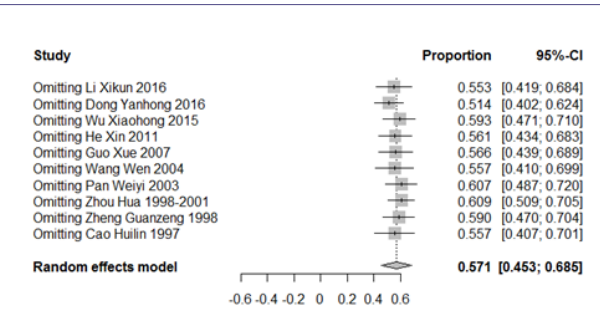

Figure 5: Sensitivity analysis for VZV prevalence in each study.

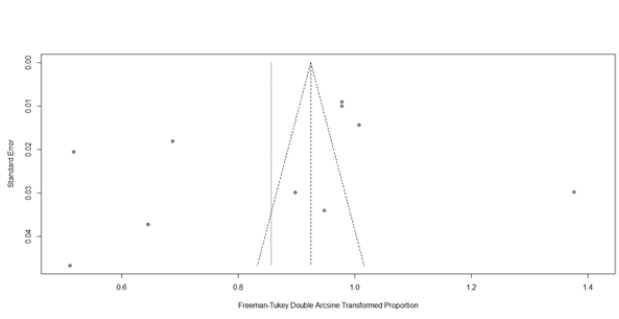

Figure 6: Begg's funnel plot with pseudo 95% confidence limits.

Discussion

Varicella or herpes zoster are acute infectious diseases caused by infection with VZV, and its prevalence is very high worldwide. Humans are generally susceptible to VZV, and 90% of the susceptible people who come into close contact with VZV are infected mainly through the respiratory tract. Immunity occurs after illness, and no secondary infection occurs. In vivo antibodies cannot eliminate latent varicella virus in the spinal nerve root ganglia, and herpes zoster can still occur many years later [21]. The predilection age of varicella is infants and children, while herpes zoster is a recurrent disease, usually seen in adults aged 40 to 70. There are more cases in spring and autumn.

Ten studies on VZV immunity prevalence were included in this meta-analysis. The results showed that the prevalence of VZV in all age stratification had greater or lesser heterogeneity. In all reports, an age-dependent pattern was demonstrated in VZV seropositivity. Seropositivity rates were low in early childhood as the frequency of positive samples was 28.38% (95% CI: 14.4%-44.8%) during the first 1-3 years. The VZV seroprevalence increased from 28.38% in 1-3 year-olds to 43.37% in 4-6 year-olds. The VZV prevalence at the age of 7-13 years old and 14-19 years old were 69.73% and 83.48%, respectively, and was approximately three times higher than that of 1-3 years old and almost two times higher than that of 4-6 years old. By the ages of 20-35 years, VZV seroprevalence of young people steeply rose to 92.26%, and at the ages of 36-45 years, 93.37% of the population had already been infected by VZV. VZV prevalence of 36-45 year-olds was close to that of 20-35 year-olds. Finally, 84.70% people were seropositive for anti-VZV antibodies beyond the age of 45, which was lower than that of the age group of 20-45 years old. There was some heterogeneity in the VZV prevalence of 1-3, 4-6, 7-13, 14-19, 36-45, and over 45 years old. A random effect model was used to analyze the data, and there was significant statistical significance. No heterogeneity was found in the statistical results of VZV prevalence between 20 and 35 years old, and a fixed effect model (I^2=0, P=0.569) was used for meta-analysis. The results of this study were consistent with those of Allami et al., [22], but the age stratification of the two studies is different. The prevalence of VZV in Iran is 89.54% in the age group of 26-30 years old, followed by 85.92% in the age group of 31-40 years old. The VZV prevalence of children in China is 28.38% in the age group of 1-3 years old, 43.37% in 4-6 years old, and 69.73% in 7-13 years old, which is higher than Iran (21.96% in 1-5 year-olds, 42.09% in 6-10 year-olds, and 59.44% in 11-15 year-olds). The prevalence of VZV in both studies over 40 years old was over 80%. It was found that the seroprevalence of VZV increased with age before the age of 45, which is in agreement with the results of Mahamud et al., [23]. Before introducing the routine varicella vaccination program, the VZV seroprevalence among students of American Samoa University and elementary school increased with age, from 76.0% at the ages of 4-6 to 97.7% by the age of 23. This is in contrast with the research results of Pinchinat et al., [5], who found that the prevalence of herpes zoster in Europe increased with age and became more serious after age 50.

There are 19 southern provinces and 15 northern provinces in China. Ten studies were distributed in six southern provinces and cities (Zhejiang, Shanghai, Fujian, Guangdong, Jiangsu, Sichuan) and four northern provinces and cities (Beijing, Liaoning, Heilongjiang, Henan). the VZV prevalence in each study was used to conduct a summary analysis with open-meta-analysis software. Eight studies were selected to independently study the prevalence rate of VZV in a certain region. The results found that compared with that in the southern region, the VZV prevalence in the northern region (Harbin 71.5%, Beijing Chaoyang 96.4% and Luohe 66.0%) was higher than that in the southern region (Fujian23.7 %, Jinhua36.1%, Shanghai 24.4%,

Hangzhou and Taizhou 58.5%, and Maoming 40.3%), which was similar to the VZV seropositive rate between tropical and temperate regions in Iraq [10].

By analyzing the influence of gender on the VZV prevalence in nine studies, it was found that the average prevalence of VZV in women was 63.81%, and that in men was 64.77%. The VZV prevalence in men was slightly higher than that in men (P>0.05, no statistical difference), which was not consistent with the results of Pinchinat et al., [5]. The prevalence of VZV in women was higher than that in men, and the difference increased with age. Compared with Amjadi et al., [24], the prevalence rate of VZV in Chinese women was 63.81%, which was lower than that in Iranian women (80.47%). Dong Yanhong et al., [15] found that the VZV prevalence of the elderly was 96.56% in Chaoyang District of Beijing, which was slightly higher than that of 95.30% in Iran. Due to the decrease of immunity, the elderly were more susceptible to VZV infection.

A total VZV seropositivity rate of 57.1% (95% CI:45.3%-68.5%) in this Chinese study was lower than Iranian (78.50%) and Polish (76.6%) rates of VZV prevalence [24,25].

Conclusion

In conclusion, according to the inclusion and exclusion criteria, this study included 10 studies on the prevalence of VZV published from 1997 to 2019 in different regions of China. Results from this study demonstrated a close relationship between seroprevalence and age, but no close correlation with gender, rural/urban areas and geographical regions of China [5]. The meta-analysis showed that the VZV seroprevalence increased with age, and there was no significant difference between different genders. The prevalence of VZV in northern areas was higher than that in southern areas. From 1997 to 2019, the VZV prevalence increased each year, so the public health prevention of VZV needs to be further strengthened. The sero-epidemiological survey of VZV is helpful to understand the status of VZV infection in healthy people and to assess the risk of herpes zoster.

Limitations of the study

The sample size of this study is small, the data is incomplete, and the research objects are different. There is some bias in the research results. We hope to obtain more research data in the future, so that the results will be more convincing.

Data Availability Statement

All data used to support the findings of this study are included within the article.

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Ethics approval and consent to participate

Not applicable.

Author's Contribution

X. Wang screened the literatures and extracted data, X. Wang and X. Shao analyzed data, L. Wang write the initial draft of the manuscript, the all authors have read and approved the final manuscript, L. Wang contributed to manuscript revisions, All authors have read and approved the manuscript.

Consent for publication

Not applicable.

Conflicts of Interest

The authors have no conflicting interests to declare.

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