Spatiotemporal Distribution of Varicella in South Korea

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Abstract

Background

Varicella is a highly contagious disease caused by the varicella-zoster virus (VZV). Given its tendency to cluster geographically, spatial analyses may provide better understanding of the pattern of varicella transmission. We investigated the spatial characteristics of varicella in Korea and the risk factors for varicella at a national level.

Methods

Using national surveillance and demographic data, we examined the spatial distribution of incidence rates and their spatial autocorrelation and calculated Moran's index. Spatial regression analysis was used to identify sociodemographic predictors of varicella incidence at the district level.

Results

An increasing tendency in the annual incidence of varicella was observed over a 12-year period (2006–2017), with a surge in 2017. There was a clear positive spatial autocorrelation of the varicella incidence rate during the surveillance period. During 2006–2014, High-High (HH) clusters were mostly confined to the northeast region and neighboring districts. Population density and the number of hospitals per 1,000 persons had negative coefficients, and the former was significant. Childhood percentage, percentage of children under 12 years of age among total population, and vaccine coverage rate had positive coefficients, but only the former was significant.

Conclusion

There was a temporal uptrend in the incidence of varicella in Korea from 2006 to 2017 in the setting of positive spatial associations. The varicella incidence according to geographic region varied with population density, childhood percentage, suggesting the importance of the community-level surveillance and monitoring strategies.

Background

Varicella is a highly contagious disease caused by the varicella-zoster virus (VZV) [1]. In South Korea, varicella vaccination was introduced to the National Immunization Program (NIP) in 2005. Nevertheless, the incidence of varicella increased from 22.5 to 154.8 cases per 100,000 persons from 2006 to 2017 [2].

As varicella tends to cluster geographically in susceptible populations residing in proximity, spatial analyses may provide better understanding of pattern of varicella transmission. This study, examined the

spatial characteristics of varicella in Korea and the risk factors for varicella at a national level.

Methods

Setting and data collection

South Korea covers 100,032 km² and had a population of approximately 52 million in 2017. It consists of 17 provinces (si-do) divided into 250 districts (si-gun-gu). Varicella was made nationally notifiable in July 2005. We used the National Notifiable Disease Surveillance System database to collect the number of reported varicella cases at the district level from January 2006 through December 2017.

Sociodemographic data on the population density, childhood percentage, percentage of children under 12 years of age among total population, number of hospitals per 1,000 persons, and vaccine coverage rate for each district were retrieved from the Korean National Statistics Office. Direct standardization was used to determine the varicella incidence rate in each district.

Statistical analysis

An epidemic curve of monthly varicella cases from January 2006 through December 2017 was drawn to reveal seasonal peaks, and the annual incidence was plotted to identify the annual trend during this periods.

To examine the spatial distribution of incidence rates and their spatial autocorrelation, we visualized the district incidence rates using a 10-color scale and calculated Moran's index. To find local clusters including 'hot spots' (high values next to high, HH), and 'cold spots' (low values next to low, LL), local indicators of spatial association (LISA) analysis was performed, and Monte Carlo simulation was used to evaluate the p -value in conducting LISA analysis.

Spatial regression analysis was performed to find sociodemographic predictors of varicella incidence at the district level. The spatial lag and spatial error model is an extension of the traditional ordinary least square (OLS) regression model that includes the spatial dependency of variables or errors in the model. The spatial lag model takes the following form:

$$Y = \rho WY + X\beta + \varepsilon$$

Where values of the dependent variable in neighboring locations (WY) are included as an extra explanatory variable. The spatial error model takes the following form:

$$Y = X\beta + \lambda W\varepsilon + u$$

Where values of the residuals in neighboring locations ($W\varepsilon$) are included as an extra term in the equation.

We used GeoDa software (version 1.12, The University of Chicago, IL, USA) to conduct the spatial analyses and QGIS software (version 3.2.1, QGIS Development Team) to visualize maps of incidence rates and local clusters.

Results

Temporal trend

The annual incidence of varicella increased over the 12-year study period, with a surge in 2017 (26,032 more cases than the previous year) (Fig. 1A). During this period, the incidence of varicella increased from 11,027 cases in 2006 to 80,092 cases in 2017, with a small dip in 2010 (797 fewer cases than the previous year) and a large dip in 2012 (8,486 fewer cases than the previous year). The monthly distribution of varicella cases had a clear seasonal pattern with two regular semesters (March–July and September–December), with a higher peak in December and a lower one in May (Fig. 1B).

Spatial Pattern

The cases of varicella in the 250 districts were summarized according to surveillance years and categorized into 17 provinces (si-do) (Table 1, Fig. 2). Figure 3 shows the incidence of varicella in the 250 districts according to surveillance year using color maps, with the provincial borders drawn in black. From 2006 to 2008, there were concentrated regional outbreaks in remote rural areas in the northeast (Gangwon-do) and south (Jeju-do). From 2009 to 2011, varicella spread slowly from the northeast to neighboring Gyeonggi-do and Chungcheongbuk-do. From 2012 to 2014, the incidence increased across Korea. In 2015 to 2017, the incidence of varicella peaked nationwide and was highest in the center-north (Yongin-si), southwest (Mokpo-si), and southeast (Busan).

Table 1
Geographical distribution of varicella cases during 2006–2017 in the republic of Korea

Province (No. of districts)	2006–2008		2009–2011		2012–2014		2015–2017	
	N	(%)	N	(%)	N	(%)	N	(%)
Total(250)	50,967	(100.0)	81,641	(100.0)	106,979	(100.0)	179,920	(100.0)
Seoul(25)	4,390	(8.6)	8,032	(9.8)	11,641	(10.9)	21,864	(12.2)
Busan(16)	6,323	(12.4)	8,942	(11.0)	8,138	(7.6)	9,934	(5.5)
Daegu(8)	3,798	(7.5)	7,927	(9.7)	7,174	(6.7)	9,458	(5.3)
Incheon(10)	4,923	(9.7)	7,370	(9.0)	7,869	(7.4)	10,406	(5.8)
Gwangju(5)	1,005	(2.0)	1,917	(2.3)	2,828	(2.6)	5,532	(3.1)
Daejeon(5)	937	(1.8)	1,913	(2.3)	2,352	(2.2)	5,686	(3.2)
Ulsan(5)	2,677	(5.3)	3,112	(3.8)	3,760	(3.5)	5,525	(3.1)
Gyeonggi(42)	12,041	(23.6)	18,356	(22.5)	28,812	(26.9)	50,580	(28.1)
Sejong(1)	0	(0.0)	0	(0.0)	128	(0.1)	1,246	(0.7)
Gangwon(18)	6,228	(12.2)	7,945	(9.7)	6,339	(5.9)	5,397	(3.0)
Chungbuk(14)	1,010	(2.0)	2,039	(2.5)	1,807	(1.7)	4,008	(2.2)
Chungnam(16)	349	(0.7)	1,981	(2.4)	4,994	(4.7)	7,200	(4.0)
Jeonbuk(15)	1,556	(3.1)	1,087	(1.3)	4,946	(4.6)	7,851	(4.4)
Jeonnam(22)	1,210	(2.4)	2,408	(2.9)	4,059	(3.8)	8,130	(4.5)
Gyeongbuk(24)	2,203	(4.3)	3,011	(3.7)	3,753	(3.5)	8,707	(4.8)
Gyeongnam(22)	938	(1.8)	2,870	(3.5)	5,984	(5.6)	14,540	(8.1)
Jeju(2)	1,394	(2.7)	2,731	(3.3)	2,395	(2.2)	3,856	(2.1)

The spatial clustering of varicella was examined using global autocorrelation analysis (Table 2). A positive spatial autocorrelation was found for the varicella incidence over the entire surveillance period. Moran's index ranged from 0.1400 to 0.3210 and was significant in all cases.

Table 2
Global spatial autocorrelation analysis of
varicella incidence in the Republic of Korea,
2006–2017

	Moran's Index	Z	<i>p</i> value
2006	0.1400	2.6566	0.019
2007	0.2443	4.9754	0.001
2008	0.2245	4.6494	0.001
2009	0.1894	3.7468	0.003
2010	0.3210	6.258	0.001
2011	0.2102	4.0321	0.003
2012	0.2880	5.393	0.001
2013	0.2768	5.285	0.001
2014	0.2201	4.2282	0.001
2015	0.1921	3.7084	0.002
2016	0.1939	3.6515	0.002
2017	0.2491	4.7742	0.001

Local spatial clusters were seen in the color maps (Fig. 4). During 2006–2014, the High-High (HH) clusters were mostly confined to Gangwon-do in the northeast and neighboring Yongin-si, Yeosu-si, Ichon-gun, and Yangpyeong-gun in Gyeonggi-do. The neighboring districts also contained ‘hot spot’ clusters during the last surveillance period of 2015–2017. The Low-Low (LL) clusters were mostly in southern Korea during the early surveillance period. Subsequently, the clusters gradually scattered and faded.

Spatial Regression Analysis

We assumed that sociodemographic factors influence the epidemics of varicella at the district level, such as population density, childhood percentage, number of hospitals per 1,000 persons, and vaccine coverage rate (Table 3). The vaccine coverage rate of each province exceeded 96%, and its geographical distribution is shown in Fig. 5. Using these variables as predictors, with annual varicella incidence as the dependent variable, we fitted a spatial regression model. The spatial error dependence was significant and explained 36.6% of the variation (Table 4), whereas the spatial lag dependence did not. Population density and number of hospitals per 1,000 persons, which is a proxy for local health infrastructure, had negative coefficients, and the former was significant. Proportion of children had a significant positive coefficient, whereas the vaccine coverage rate, which was categorized into four ordinal values based on the quartiles of its distribution to avoid multicollinearity, had a non-significant positive coefficient.

Table 3

Varicella incidence rate and sociodemographic predictors during 2012–2017 in the republic of Korea

Province (No. of districts)	Incidence rate (per 100,000)	Population density (No. of person/km ²)	Childhood percentage (%)	Number of hospitals (per 1,000)	Vaccine coverage rate (%)
Total(250)	93.5	511.9	11.9	1.7	97.3
Seoul(25)	55.7	16653.8	10.4	2.1	96.2
Busan(16)	85.0	4571.9	10.0	1.8	96.8
Daegu(8)	111.0	2823.3	11.4	1.9	97.6
Incheon(10)	104.9	2765.7	12.2	1.4	97.7
Gwangju(5)	94.7	2936.8	13.4	1.8	98.2
Daejeon(5)	88.0	2824.8	12.9	1.9	97.7
Ulsan(5)	133.1	1096.7	13.0	1.5	98.4
Gyeonggi(42)	104.3	363.7	8.9	1.4	98.3
Sejong(1)	108.0	1217.2	13.2	1.5	97.4
Gangwon(18)	126.9	91.9	11.0	1.5	97.9
Chungbuk(14)	65.5	213.1	14.1	1.8	98.1
Chungnam(16)	98.2	251.2	12.5	1.6	98.0
Jeonbuk(15)	114.2	231.9	11.7	1.9	97.7
Jeonnam(22)	106.7	155.0	11.1	1.7	98.0
Gyeongbuk(24)	76.8	141.9	11.0	1.6	97.8
Gyeongnam(22)	102.2	317.8	12.6	1.4	97.7
Jeju(2)	168.8	330.0	13.6	1.7	97.0

Table 4

Spatial regression of sociodemographic predictors of varicella incidence in the Republic of Korea, 2012–2017

Variable*	Coeff.	S.E.	P value	AIC	R-squared
Constant	59.4212	12.5438	0.0000	2491.9	0.3658
Population Density	-0.0010	0.0005	0.0352		
Childhood Percentage [†]	321.25	83.276	0.0001		
No. Hospitals per 1,000 person	-6.2536	3.6413	0.0859		
Vaccine Coverage Quartile [§]	4.3670	2.4043	0.0693		
Lambda	0.4731	0.0546	0.0000		
* Data of sociodemographic predictors in 2017 were missing and vaccine coverages were only available during 2015–2017. Spatial error model was fitted.					
[†] Percentage of children under 12 years of age among total population					
[§] Vaccine coverage quartile(min: 0.9363, Q1: 0.9697, Q2: 0.9758, Q3: 0.9800, max: 0.9897) was used to avoid multicollinearity problem.					

Discussion

In this study, we found a temporal uptrend in the incidence of varicella in Korea from 2006 to 2017 in the setting of positive spatial associations confined to the northeast (Gangwon-do) that gradually spread and faded over time, which led to an overall increase in varicella incidence across the country. The upward trend in varicella in Korea despite the adoption of universal one-dose vaccination is consistent with previous studies, which have suggested insufficient effectiveness of the vaccine. In a population-based study, the effectiveness of the varicella vaccine was 13% (95% CI: – 17.3 to 35.6), and the immunity waned rapidly 3 years after vaccination [3]. Furthermore, a population-based study of the effectiveness of one-dose varicella vaccination on disease severity suggested that one-dose varicella vaccination resulted in milder symptoms, resulting in failure to isolate patients, leading in turn to outbreaks among those in close contact, such as children in kindergarten or elementary school [4].

This is the first study to investigate the spatial epidemic characteristics of varicella on a nation-wide scale. Nevertheless, the occurrence of local ‘hot-spots’ in remote areas, such as Gangwon-do, may be similar to the results of studies on a province scale or of other respiratory diseases, such as mumps and measles. A spatiotemporal analysis of varicella in Valencia, Spain from 2008 to 2012 identified spatiotemporal clusters where the population was economically disadvantaged or perhaps less educated and less aware of vaccination schedules [5]. In spatio-temporal analysis of measles [6] and mumps [7] in China, high-risk clusters were mainly distributed in the urban-rural transition zones or semi-urban areas because, with

parents migrating to urban areas for employment opportunities, children were left in impoverished and remote area from vaccination clinics and become susceptible to disease.

We also found that the childhood percentage had a positive effect on the incidence of varicella at the district level, whereas population density and number of hospitals per 1,000 persons had negative effects. The spatial regression revealed that childhood percentage, a high-risk population, influenced the incidence of varicella. In our study, childhood percentage showed vulnerability to varicella outbreaks. This concurs with a previous study conducted APC analysis of varicella incidence in Korea [8], in which the peak incidence was 4–6 years of age. In a spatial analysis of mumps in Korea, childhood percentage was a significant risk factor for mumps because children are more susceptible than other age groups [9].

The number of hospitals per 1,000 persons in a district, which we used to indicate the health infrastructure, also had affected the incidence of varicella, albeit not significantly (p -value = 0.0693). The fewer healthcare providers in a district, the higher the varicella incidence. This may be associated with the low economic status of a district, in accordance with the results of the spatial analysis mentioned above.

The lack of a relationship between the vaccine coverage rate and incidence of varicella may be explained by the high level of coverage, ranging from 92.3–100%. Given the high vaccination coverage in Koreans before the introduction of a universal one-dose varicella vaccination in 2005, the vaccine may not have affected the incidence of varicella greatly.

Our study had several limitations. First, given the data was obtained from passive collected surveillance system, there may be underreported cases especially those with mild breakthrough infections. Second, varicella cases were obtained from aggregate data at the district level, and not from individuals because of the inaccessibility of personal information. Factors such as vaccination coverage, disease severity, and socioeconomic status at the individual level, which may drive a varicella epidemic were not included in the spatial regression model and have yet to be examined in detail. Finally, there might be multicollinearity among the predictors of varicella incidence. Despite these limitations, this study is the first to describe the spatial epidemiological characteristics of varicella using spatial analysis at the district level in Korea, and it identified high-risk clusters and risk factors.

Conclusions

We examined the spatiotemporal pattern of varicella in the Republic of Korea over the past 12 years. The varicella incidence according to geographic region varied with population density, childhood percentage in the district and neighboring regions, suggesting the importance of community-level surveillance and monitoring to prevent and control varicella.

Abbreviations

VZV

varicella-zoster virus

NIP

National Immunization Program

HH

High values next to high (High-High)

LL

Low values next to low (Low-Low)

LISA

Local Indicators of Spatial Association

OLS

Ordinary Least Square

Declarations

Ethics approval and consent to participate

The present study protocol was reviewed and approved by the Research Ethics Board of Seoul National University (IRB No. E 1811/001–017).

Consent for publication

Not applicable.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

All authors attest they meet the ICMJE criteria for authorship.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

All authors made substantial contributions as follows: Conceptualization and conceived the study: YHL, SIC; supervised all aspects of this study: SIC; analyzed the data and Writing - original draft: YHL; Writing - review & editing: YJC, SSH; gave the critical comments on the manuscript: YJC, SSH, SIC. All authors have reviewed and approved the final version of the manuscript.

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Figures

Figure 1

Annual trend in varicella incidence during 2006-2017 and epidemic curve of monthly varicella cases in the Republic of Korea, between January 2006 and December 2017. (a) is for trend line, and (b) is for epidemic curve.

Figure 2

The map of 17 provinces in the Republic of Korea. (QGIS software version 3.2.1)

Figure 3

Incidence rate per 100 000/year of varicella in the Republic of Korea, 2006-2017. (QGIS software version 3.2.1)

Figure 4

Cluster map of varicella incidence rate in the Republic of Korea, 2006-2017.(QGIS software version 3.2.1and GeoDa software version 1.12)

Figure 5

Map of average of vaccination coverage rates in the Republic of Korea, 2015–2017. (QGIS software version 3.2.1)